PSEUDOCYCLIC BENZIODOXOLE TRIFLATE AS AN EFFECTIVE REAGENT FOR THE CATALYTIC OXIDATIVE CYCLOADDITIONS OF ALDOXIMES WITH NITRILES AND MALEIMIDES

A THESIS

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Dedicated to my parents

and my brother

for their endless love and sacrification

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LIST OF SYMBOLS AND ABBREVIATIONS

HTIB: Hydroxy(tosyloxy)iodobenzene

DIB: (Diacetoxyiodo)benzene

PIFA: Bis(trifluoroacetoxy)iodobenzene

IBA: 2-Iodosylbenzoic acid

IBX: 2-Iodoxybenzoic acid

DMP: Dess-Martin Periodinane

IBA-OTf: 2-[Hydroxy(trifluoromethanesufonyloxy)]iodobenzoic acid

p-TsOH: p-Toluenesulfonic acid

MO: Molecular Orbital

HOMO: Highest Occupied Molecular Orbital

LUMO: Lowest Unoccupied Molecular Orbital

FMO: Frontier Molecular Orbital Theory

TfOH: Trifluoromethanesulfonic acid (triflic acid)

m-CPBA: *m*-chloroperoxybenzoic acid

DMF: Dimethylformamide

TFE: 2,2,2-Trifluoroethanol

TFA: Trifluoroacetic acid

HFIP: Hexafluoroisopropanol

THF: Tetrahydrofuran

DCM: Dichloromethane

DMSO: Dimethyl sulfoxide

NBS: *N*-Bromosuccinimide

LiHMDS: Lithium hexamethyldisilazide (lithium bis(trimethylsilyl)amide)

NMR: Nuclear Magnetic Resonance

ESI-MS: Electrospray Ionization Mass Spectrometry

HR-MS: High-Resolution Mass Spectrometry

IR: Infrared

TMS: Tetramethylsilane

LCD: Liquid Crystal Display

IUPAC: The International Union of Pure and Applied Chemistry

1. PREFACE

Since the first hypervalent organoiodine reagent, (dichloroiodo)benzene, was synthesized in 1886, those compounds have increasingly gained more and more attention in organic chemistry due to their synthetic versatility. Moreover, their similarity in reactivity to transition metal complexes made these hypervalent organoiodine compounds preferred as green alternatives to limit the negative impact on the environment. In addition to well-known commercially available hypervalent iodine compounds such as DIB, PIFA, HTIB (Koser's reagent), DMP, and IBX, hundreds of other hypervalent iodine compounds have been continuously studied in the scope of preparation, structural and property determination, and reactivity as reagents or catalysts in various transformations such as halogenation, oxidation and oxidative functionalization, azidation, amination, rearrangement, etc. As a part of our ongoing research of finding new hypervalent organoiodine reagents, we studied the reactivity of 2-[hydroxy(trifluoromethanesufonyloxy)]iodobenzoic acid (IBA-OTf) in the oxidative cycloaddition of benzaldoximes with acetonitrile and maleimide to prepare substituted 1,2,4-oxadiazoles and bicyclic isoxazolines, respectively. The reactions were performed in the catalytic manner where IBA-OTf can be generated *in situ* from a small amount of 2-iodobenzoic acid (5-10 mol %). However, the isolated yields of investigated products were comparable with those obtained using a stoichiometric amount IBA-OTf as reported previously.

2. BACKGROUNDS

2.1. General information on iodine and its common applications

Elemental iodine was first isolated in 1811 from seaweed ashes by French chemist Bernard Courtois. Since then, iodine compounds have found numerous applications in many fields, especially in medicine and pharmaceuticals. For example, potassium iodide is used to treat acute thyrotoxicosis as well as to limit the radioactive exposure of iodine-131 from nuclear crises or radiopharmaceutical therapy. Due to its strong interaction with X-ray, many iodine-based X-ray contrast agents were also developed and have been used commonly in medicine to enable the visualization of soft tissues in X-ray imaging. The solution of elemental iodine and potassium iodide in alcohol is well known for its antimicrobial activity. Other applications include the using of copper iodide as stabilizer for thermoplastic nylon production, rhodium- and iridium iodide complexes as the catalysts for the industrial scale manufacture of acetic acid, polyiodides incorporated into polyvinyl alcohol as polarizing film for LCD screens, and iodine-based biocides as additives to cosmetics, paints, inks, wood, etc. for preservation purpose.[1-4] In organic chemistry, elemental iodine as well as iodide compounds have also gained numerous applications, mainly as catalysts and pre-catalysts for various oxidative transformations. Their activity in some way resembles that of transition-metallic catalysts. However, non-toxic property and inexpensive source of supply of iodine-based catalysts have made them increasingly favorable from the viewpoint of sustainable chemistry.[5, 6]

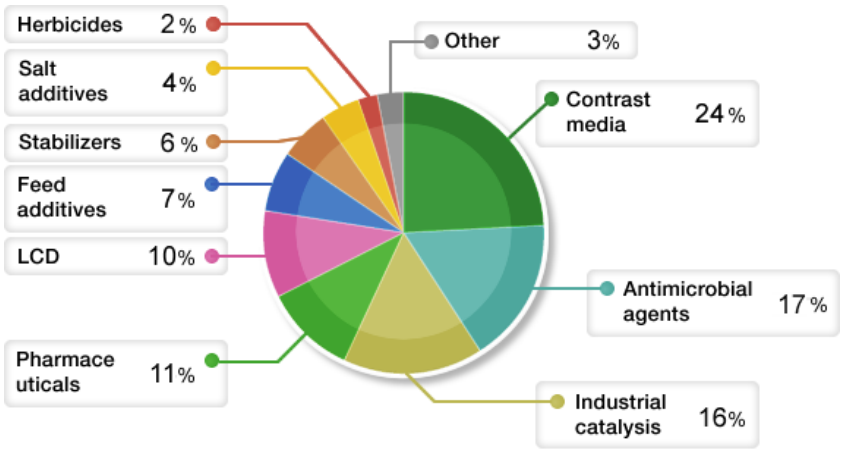


Figure 1. The usage of iodine in different fields.[4]

2.2. General information on hypervalent iodine compounds

2.2.1. Definition, classification, and geometry

According to IUPAC, hypervalency is the ability of an atom in a molecular entity to expand its valence shell beyond the limits of the Lewis octet rule. Hypervalent compounds are common for the second and subsequent row elements in groups 15–18 of the periodic table.[7] Among these, hypervalent iodine compounds have gained much attention due to their versatility in organic syntheses. Fundamentally, they can be used as substrates, reactants, reagents, or catalysts for various organic reactions, such as halogenation, oxidation and oxidative functionalization, azidation, amination, rearrangement, etc.[2]

In general, hypervalent iodine compounds are classified into seven types whose structures are shown in Figure 2. Species **1**, iodonium salts, in some aspects, can be commonly considered as trivalent iodine compounds when the presence of a loose coordination bond between the central iodine atom and the counter anion was confirmed by X-ray crystallography. Therefore, together, species **1-3** are placed into the same group of trivalent iodine (iodinanes) in which the oxidation state of central iodine atom is +3. Species **4** and **5** whose central iodines have the oxidation state of +5 are classified as pentavalent iodines (periodinanes). A large variety of trivalent and pentavalent organoiodine compounds have been successfully prepared, characterized, and tested for their application in organic synthesis (Figure 3). Meanwhile, for heptavalent iodine species **6** and **7**, there have been only several inorganic compounds of iodine (VII) reported, such as IF_7, IO_2F_3, IOF_5, and the derivatives of HIO_4.[2]

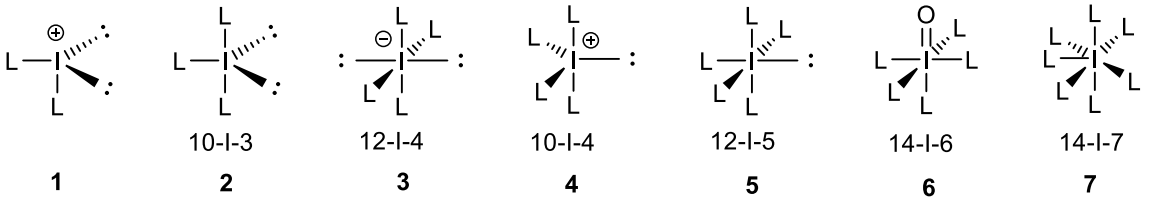


Figure 2. Martin-Arduengo classification of hypervalent iodine species.[2]

Depending on the oxidation state of the iodine center and the number of ligands surrounding it, the geometry of hypervalent iodine compounds can be various. Trivalent

iodine compounds $ArIL_2$ have trigonal bipyramidal geometry with sp^2-hybridized iodines at the center. Two lone pairs of electrons and the aryl substituent occupy equatorial positions while two heteroatomic ligands L are located at apical positions. The overlapping between two ligand orbitals and a filled 5p orbital of central iodine establishes a linear three-center four-electron hypervalent bond consisting three new molecular orbitals: bonding, nonbonding, and antibonding. The presence of a node at central iodine in the nonbonding molecular orbital make the hypervalent bond more polarized, longer and weaker than a normal covalent bond. As a result, two apical ligands are relatively labile, making the electron-deficient iodine center more susceptible to nucleophilic attack by various substrates to finally afford corresponding oxidative products after further consecutive steps.

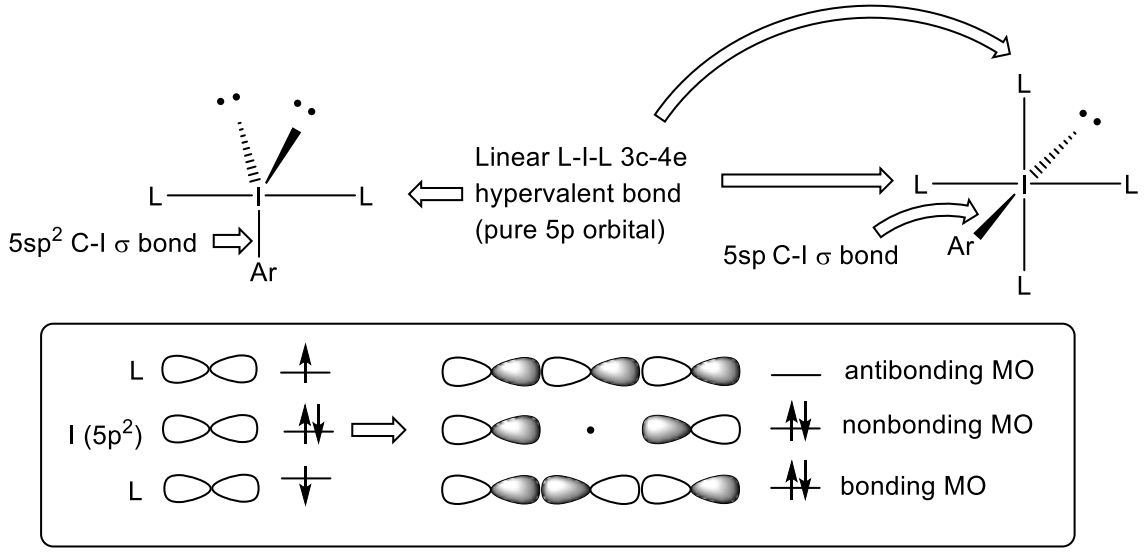


Figure 3. Bonding in trivalent and pentavalent iodine compounds and the molecular orbital description of a hypervalent bond.

In a similar way, the molecular geometry of iodonium salts (typically Ar_2IX) was also identified as a distorted pseudo-trigonal bipyramid by single X-ray crystallographic studies when associated anions were found to be able to bond loosely to iodine atom. Meanwhile, the onium salts of other elements from the second and the third rows of the periodic table, such as ammonium, oxonium, phosphonium, and sulfonium salts, most likely exist in tetrahedral geometry.

The bonding in pentavalent iodine compounds $ArIL_4$ takes the shape of square bipyramid in which one sp-hybridized orbital of the central iodine is used to make a bond with the aryl moiety, and four heteroatomic ligands are distributed on two perpendicular 3c-4e hypervalent bonds.

2.2.2. Common classes of hypervalent organoiodine compounds

Trivalent iodine compounds are most commonly studied for their preparation, structure and synthetic applications with a large number of representatives being commercially available. Iodosylarenes, [bis(acyloxy)iodo]arenes, and [hydroxy(sulfonyloxy)iodo]arenes are generally used as the reagents for oxidation as well as oxidative functionalization of various organic substrates. Some important representatives of [bis(acyloxy)iodo]arenes and [hydroxy(sulfonyloxy)iodo]arenes are commonly commercially available, such as DIB, PIFA, and Koser's reagent. Meanwhile, the typical iodosylarene derivative, iodosylbenzene, is mainly prepared in laboratory scale for very few studies on the synthetic application due to its extremely poor solubility in most common organic solvents except for methanol and DMSO. (Difluoroiodo)arenes and (dichloroiodo)arenes are used as fluorinating and chlorinating reagents, respectively.[8, 9]

Cyclic trivalent iodine compounds exhibited better stability than their acyclic analogues due to the effective overlapping of two sp^2-hybridized lone pairs of electrons in iodine center with the π-electron system in the aromatic ring. Among a large variety of cyclic trivalent iodine compounds, benziodoxes have gained a lot of interest in organic synthesis as versatile reagents for multiple oxidative functionalizations of various substrates in which the heteroatomic ligands are transferred from trivalent iodine species to organic substrates.[8, 9]

Iodonium salts, in general, react with organic substrates in an entirely different way compared to the above listed trivalent iodine reagents. They have found broad application in alkylation, alkenylation, alkynylation, and arylation of various organic and inorganic substrates in a mild and highly selective manner. Specifically, iodonium ylides and iodonium imides are considered as excellent carbene and nitrene precursors, respectively.[8,10]

Compared with trivalent iodine compounds, pentavalent iodine compounds are less common in terms of the number of synthesized reagents. The typical noncyclic iodylbenzene can be used as an oxidizing reagent in spite of its explosive nature at elevated temperature and poor solubility in most common organic solvents. These drawbacks are also noted for IBX while moisture sensitivity is the major problem for the storage of DMP. Similar the other hypervalent iodine reagents, IBX and DMP along with their derivatives have also found much application in a variety of organic oxidative transformations.[9, 11]

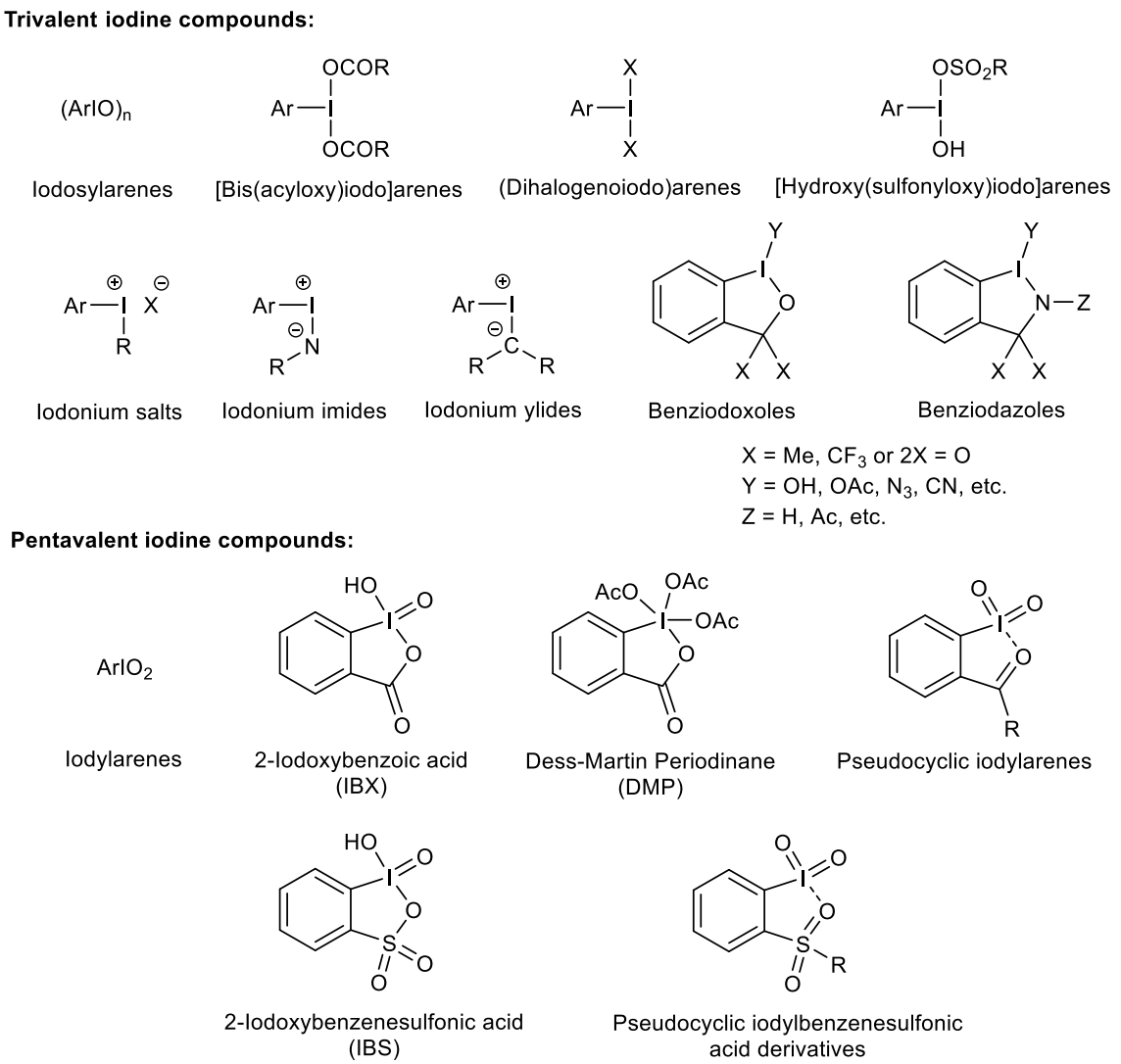
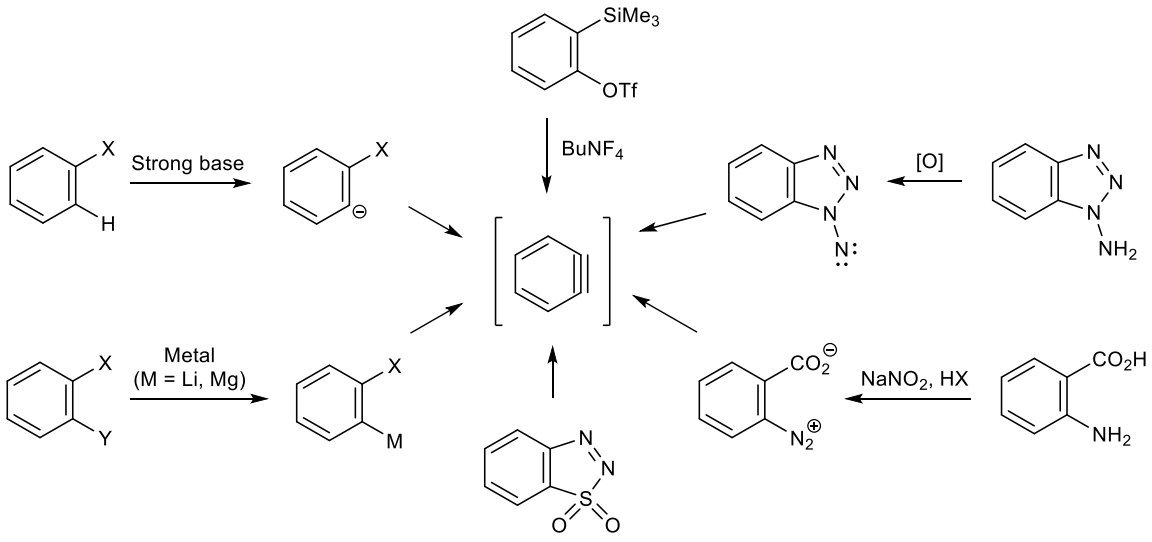


Figure 4. Common classes of hypervalent organoiodine compounds.[9]

2.3. Trivalent iodine reagent-mediated cycloadditions

2.3.1. Cycloaddition via benzyne intermediate

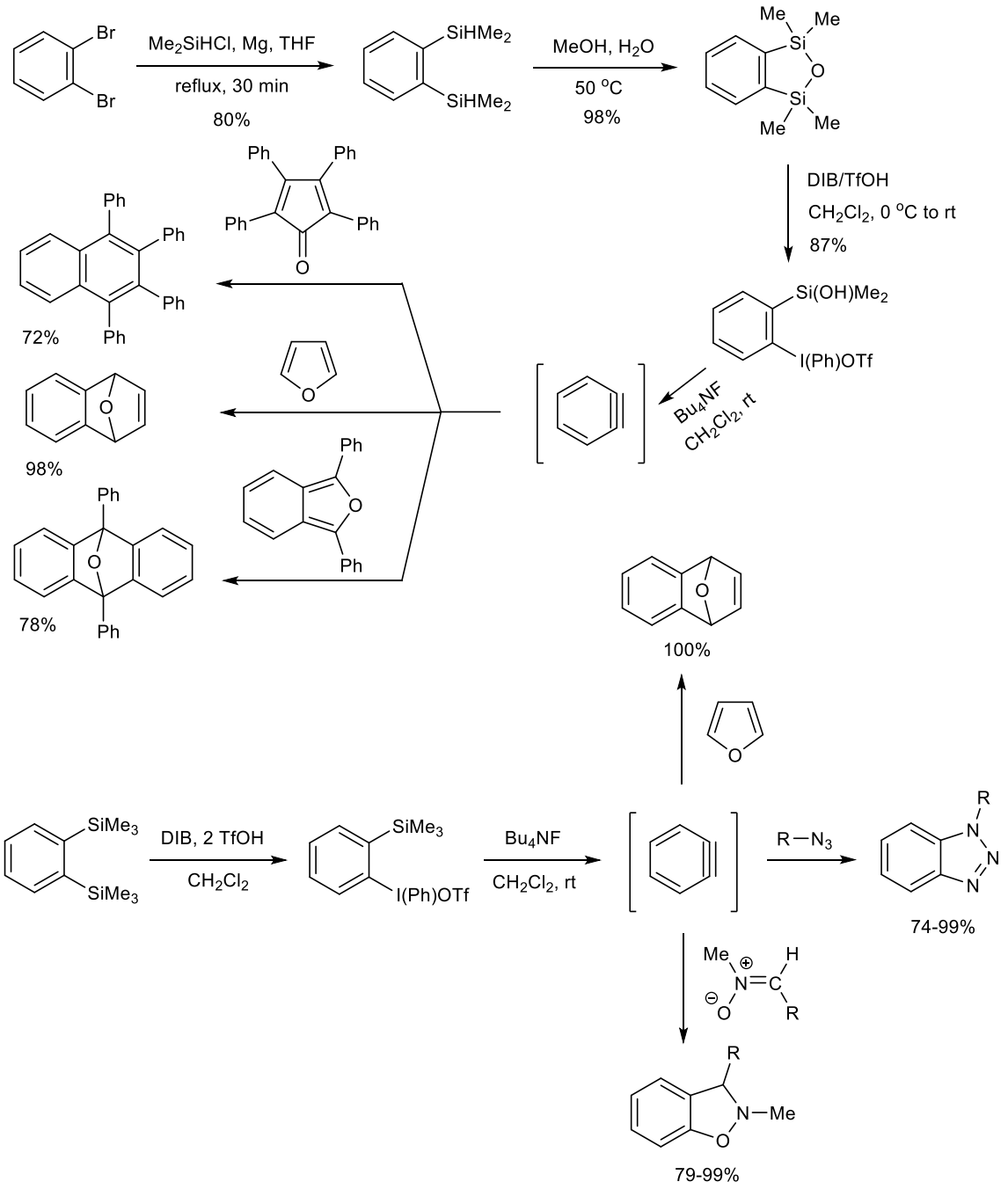
Due to its instability, benzyne can be only generated *in situ* according to some common methods depicted in Scheme 1. The generation of benzyne by treatment of an aryl halide with a strong base suffers an unavoidable drawback where the strong base can compete against nucleophiles in the reaction with benzyne. This advantage can be overcome by the treatment of *o*-dihalosubstituted benzene with an active metal (lithium or magnesium) to produce the desired benzyne after the elimination. Benzynes may also be obtained in high yields from the precursors such as 1-aminobenzotriazole, anthranilic acid, and 1,2,3-benzothiadiazole 1,1-dioxide. However, these methods are unfavorable from the viewpoint of safety because of their explosive nature. The Kobayashi protocol, in which benzynes are generated from 2-(trimethylsilyl)phenyl triflates under mild condition (at ambient temperature in neutral medium), has been considered as an alternative to afford benzynes in good yields.[12]



Scheme 1. General methods for the preparation of benzynes.[12]

Similarly, [2-(trimethylsilyl)phenyl]iodonium triflates can also generate benzyne intermediates quantitatively under mild conditions. Therefore, in comparison with previous methods (treating aryl halides with strong bases or using potentially explosive precursors such as arenediazonium-2-carboxylates, 1-aminobenzotriazole, and 1,2,3-

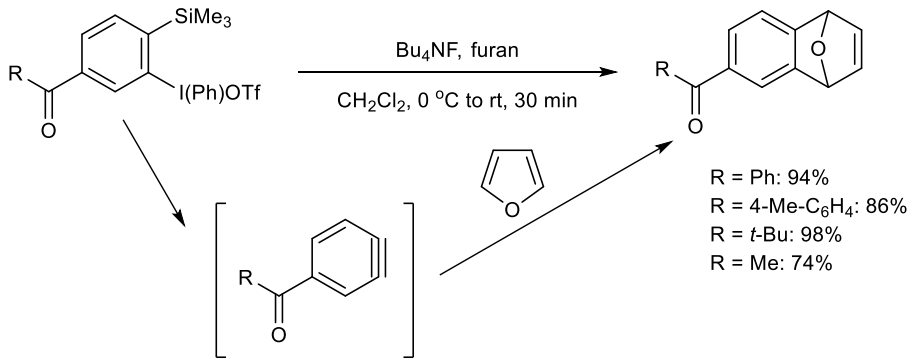
benzothiadiazole 1,1-dioxide), this method provided a more convenient way to generate benzyne in a manner where side reactions (addition to anions or dimerization) were limited, and safety issues were resolved.



Scheme 2. Synthesis of [2-(trimethylsilyl)phenyl]iodonium triflates and its application in cycloaddition via benzyne intermediate.[13, 14]

Kitamura *et al*. studied the cycloaddition of benzyne generated *in situ* by a simple treatment of [2-(trimethylsilyl)phenyl](phenyl)iodonium triflate or [2-(hydroxydimethylsilyl)phenyl](phenyl)iodonium triflate with Bu_4NF in the presence of various trapping agents (Scheme 2). All the reactions were conducted at room temperature within a short time from 20 to 30 min to afford the corresponding heterocyclic products in good yields (72-98%). The hypervalent iodine reagent can be obtained from 1,2-dibromobenzene through a three-step protocol in the total yield of 68%.[13, 14]

The reaction scope of this method was also broadened to benzyne precursors bearing reactive functional groups which are not tolerable under harsh conditions in other methods. Specifically, the treatment of [5-acyl-2-(trimethylsilyl)phenyl]iodonium triflates with $BuNF_4$ in the presence of trapping agent furan afforded the desired cycloadducts in good yields (74-94%).[15]

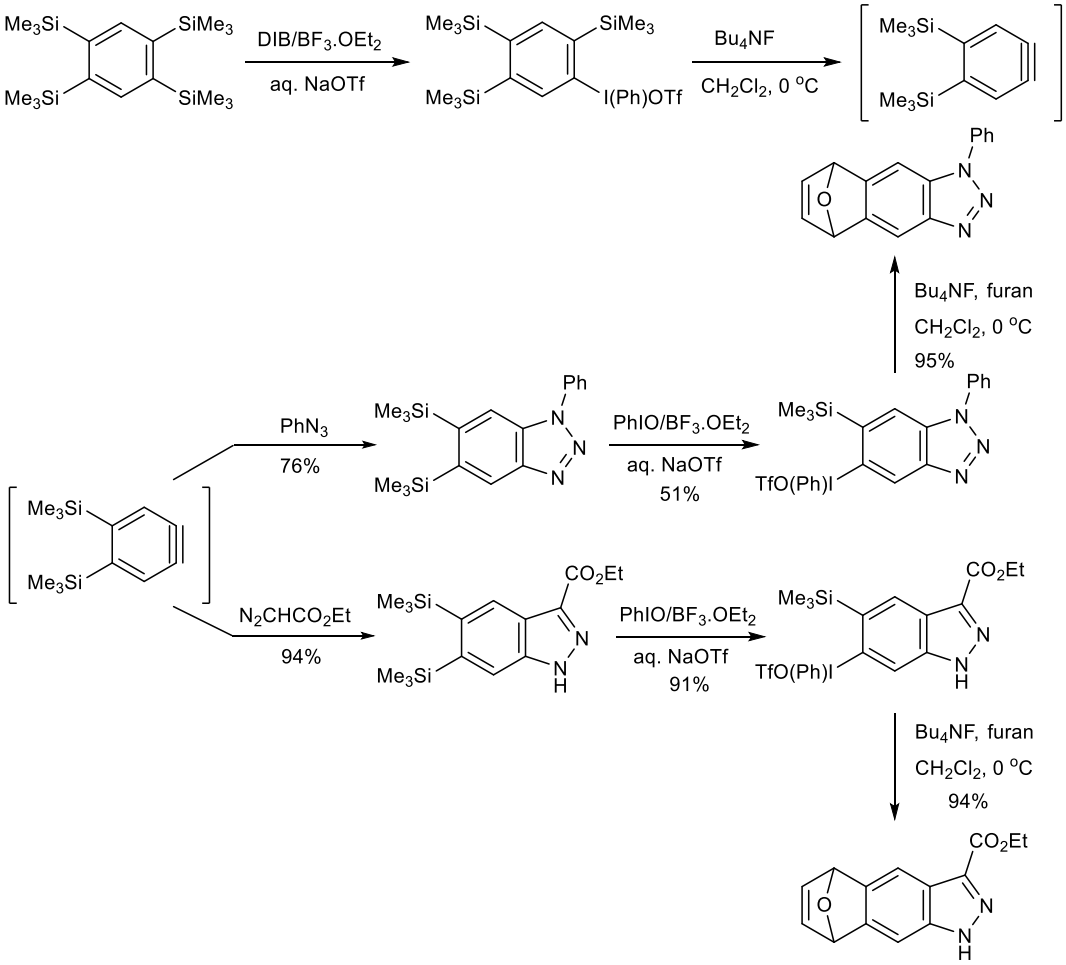


Scheme 3. Generation of acylbenzynes from hypervalent iodine compounds and their cycloaddition with furan.[15]

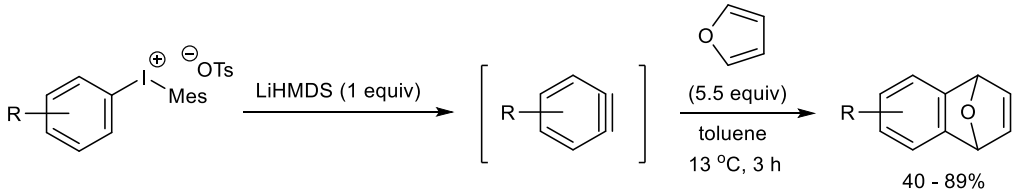
Interestingly, bis-heterocyclic compounds were also successfully synthesized from 1,2,4,5-tetrakis(trimethylsilyl)benzene via two benzyne intermediates. The triazole or diazole moiety was first incorporated into the benzene ring by 1,3-dipolar cycloaddition to produce benzotriazole and indazole, respectively, which then further converted into bis-heterocyclic compounds by another benzyne-mediated cycloaddition to furan.[16]

Recently, Stuart *et al.* demonstrated the reactivity of various unsymmetrical aryl(mesityl)iodonium salts towards Diels-Alder cycloaddition with furan. As expected,

the reactions proceeded via the reactive benzynes which were generated *in situ* from the corresponding iodonium salts under the presence of a stoichiometric quantity of LiHMDS.[17]



Scheme 4. Multistep process for the preparation of bi-heterocyclic compounds via benzyne-mediated cycloadditions.[16]



R = 4-F, 4-Br, 4-TfO, 3-Cl, 3-Br, 3-I, 4-CF_3, 4-SF_5, 3-SF_5, 4-CN, 3-CN, 3-Br-4-Me,3-Cl-4-F, 3-Cl, 6-chloropyridin-3-yl, 4-isobutyl, 4-Ph, 4-MeO, 2-naphthyl, 3-NO_2-4-Me, 3-Cl-4-MeO, 2,3-Cl_2

Scheme 5. Diels-Alder cycloaddition of unsymmetrical aryl(mesityl)iodonium salts with furan via benzyne intermediates.[17]

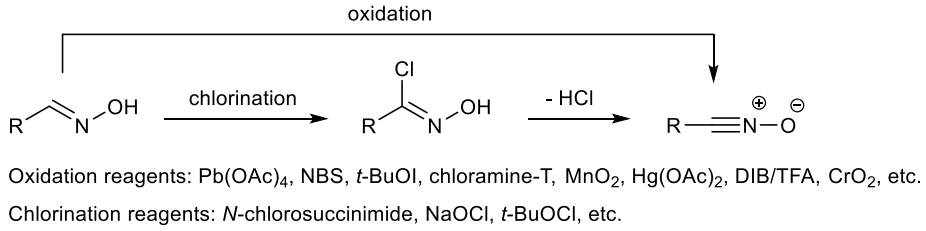
2.3.2. Cycloaddition via nitrile oxide intermediate

2.3.2.1. Common methods for nitrile oxide preparation

❖ **From aldoxime**

Under some circumstances, nitrile oxides can be easily generated from the corresponding aldoxime through direct oxidation or consecutive halogenation-dehydrohalogenation process via the intermediate hydroxymoyl halides. For the direct oxidation, some trivalent iodine compounds were reported as oxidants which can efficiently convert aromatic aldoximes into the corresponding nitrile oxides.

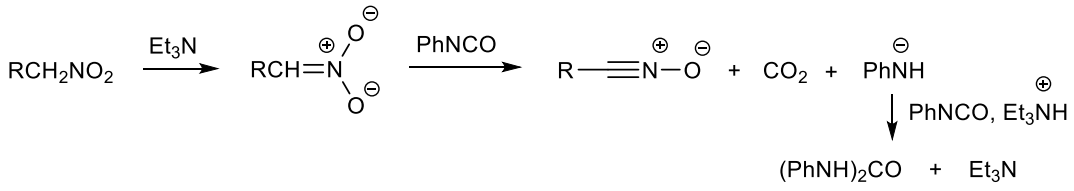
Hydroximoyl halides, typically hydroximoyl chlorides, can be obtained from aldoximes under the presence of chlorine-containing oxidants such as *N*-chlorosuccinimide, *t*-BuOCl, and NaOCl. The subsequent dehydrochlorination in a basic medium affords the desired nitrile oxides.[18, 19]



Scheme 6. Generation of nitrile oxides from aldoximes and hydroximoyl chlorides.

❖ **From nitro compounds**

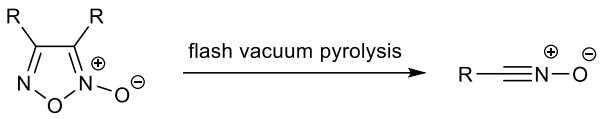
Generally, nitrile oxides can also be obtained by the dehydration of primary aliphatic nitro compounds according to the Mukaiyama procedure in the presence of aryl isocyanate and Et_3N as the reagent and the catalyst, respectively. Various other reagents, such as $POCl_3$, AcCl, Ac_2O, BzCl, $SOCl_2/Et_3N$, and $MeSO_2Cl$, were also tested for the dehydration of nitroalkanes.[18, 19]



Scheme 7. Generation of nitrile oxides from primary nitro compounds.[18]

❖ **From furoxans – the dimerization form of nitrile oxides**

Some stable commercially available furoxans are considered as the starting materials for generating unstable nitrile oxides by thermolysis or photolysis. In the presence of trapping agents, further reactions will proceed, such as cycloaddition with trapping agents or conversion to bisisocyanate. Not only furoxans but also other five-membered heterocycles including isoxazolines, 1,2,4-oxadiazoles, and furazans can be used for the cycloreversion to generate nitrile oxides.[18, 19]

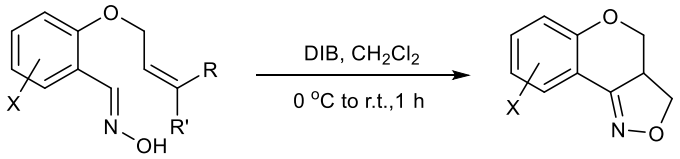


Scheme 8. Generation of nitrile oxides from furoxan by cycloreversion.[19]

2.3.2.2. Hypervalent iodine compounds as the reagents for generating nitrile oxides

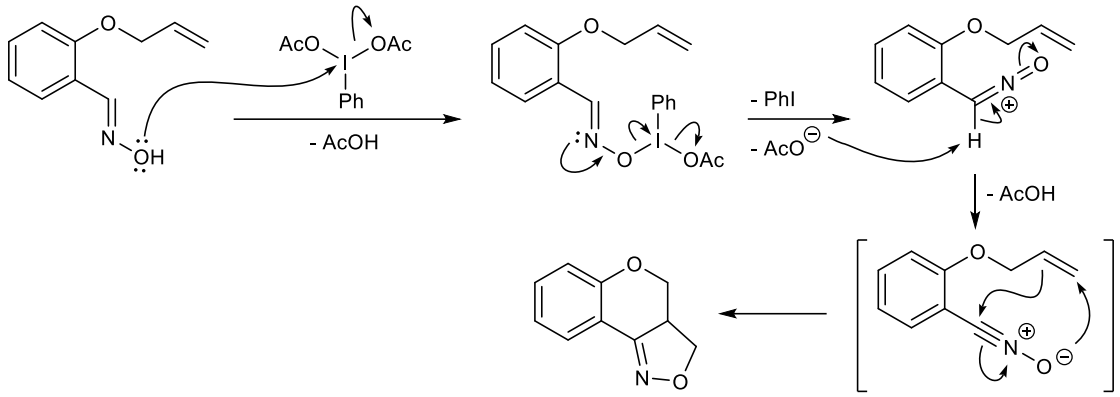
2.3.2.2.1. Intramolecular cycloaddition via nitrile oxides

In 2005, Bandgar *et al.* reported the formation of benzopyrano- and furopyrano-2-isoxazolines through the intramolecular 1,3-dipolar cycloaddition of 2-allyloxybenzaldoximes and 3-*O*-allyl-1,2-isopropylidene-furanose-5-aldoximes, respectively, in the presence of DIB in CH_2Cl_2. All the reactions were carried at 0 ^oC to room temperature within 1 h to afford the desired product in high isolated yield from 74 to 90%.[20]



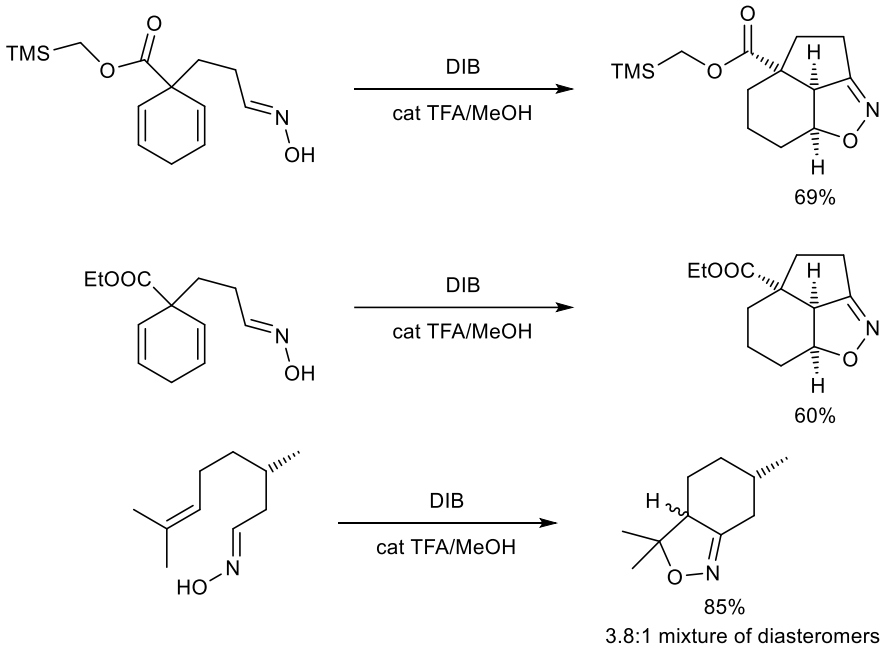
X = H, R = R'= H: 90%
X = 4-Br, R = R' = H: 80%
X = 4-Me, R = R' = H: 85%
X =2-NO_2, R = R' = H: 82%
X= 4-Cl, R = R' = H: 82%
X = H, R = R' = Me: 80%
Aldoxime = 3-*O*-allyl-1,2-*O*-isopropylidene-furanose-5-aldoxime: 76%
Aldoxime = 3-*O*-prenyl-1,2-*O*-isopropylidene-furanose-5-aldoxime: 74%

Scheme 9. The DIB-mediated formation of benzopyrano- and furopyrano-2-isoxazolines.[20]

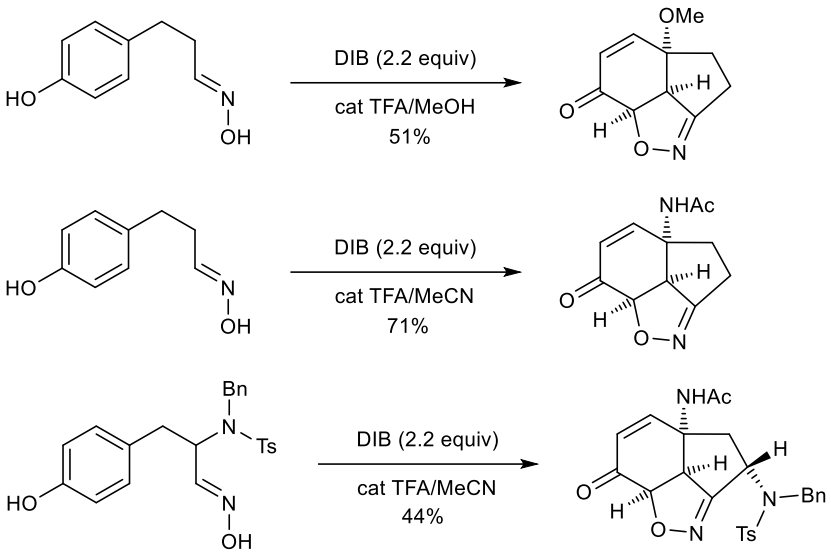


Scheme 10. The proposed mechanism for intramolecular cycloaddition 2-allyloxybenzaldoximes.[20]

The oxidative activity of DIB towards intramolecular 1,3-dipolar cycloaddition was also tested using polar solvents such as MeOH and MeCN in the presence of catalytic amount of TFA. The reaction scope was expanded to various aldoximes. Remarkably, the oxidative dearomatization of aldoximes bearing phenolic moieties was also recorded.[21]

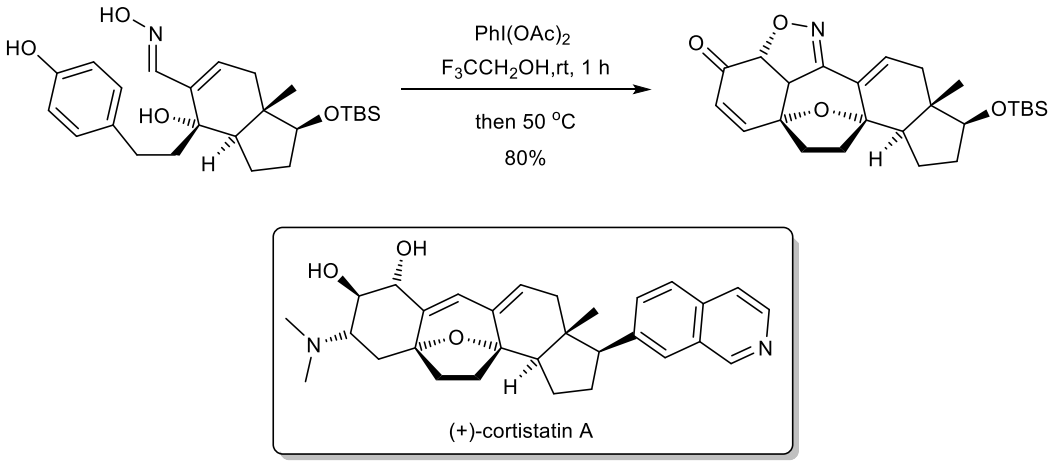


Scheme 11. The DIB-mediated intramolecular cycloadditions in catalytic TFA/MeOH.[21]



Scheme 12. Tandem oxidative methoxylation and oxidative amidation under the presence of DIB.[21]

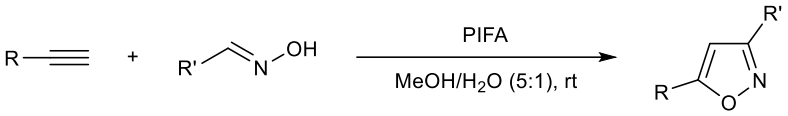
Interestingly, the pentacyclic core structure of cortistatins - a group of biologically active steroidal alkaloids isolated from the Indonesian marine sponge *Corticium simplex* - was stereoselectively synthesized through a multistep process in which the tandem oxidative dearomatization/intramolecular 1,3-dipolar cycloaddition was considered as a keystone reaction. DIB was again used as an oxidative reagent to induce the generation of nitrile oxide.[22]



Scheme 13. The hypervalent iodine-mediated synthesis of the pentacyclic core structure of cortistatins.[22]

2.3.2.2.2. Cycloaddition with alkynes

In 2011, Jawalekar *et al.* reported a mild procedure to prepare various substituted isoxazoles by cycloaddition between terminal alkynes and nitrile oxides which are generated *in situ* from corresponding aldoximes in the presence of PIFA as an oxidant. The reactions were performed in MeOH/H_2O at room temperature to give various di-substituted isoxazoles with the yield ranging from 10 to 94%. Remarkably, there was no competitive cycloaddition of nitrile oxides to olefins in case of *trans*-cinnamaldoxime.[23]



R = Ph, R' = Ph: 90%
R = 2-pyridyl, R' = Ph: 80%
R = 4-MeO-C_6H_4,R' = Ph: 81%
R = 6-hydroxy-*n*-butyl, R' = Ph: 49%
R = Ph, R' = *n*-propyl: 76%
R = 2-pyridyl, R' = *n*-propyl: 90%
R = 4-MeO-C_6H_4,R' = *n*-propyl: 60%
R = 6-hydroxy-*n*-butyl, R' = *n*-propyl: 10%
R = Ph, R' = cinnamyl: 82%
R = 2-pyridyl, R' = cinnamyl: 72%
R = 4-MeO-C_6H_4, R' = cinnamyl: 65%
R = 6-hydroxy-*n*-butyl, R' = cinnamyl: 61%
R = Ph,R' = 4-MeO-C_6H_4: 71%
R = 6-hydroxy-*n*-butyl, R' = 4-MeO-C_6H_4: 67%
R = Ph, R' = 4-tolyl : 72%
R = 6-hydroxy-*n*-butyl, R' = 4-tolyl: 66%
R = Ph, R' = 4-O_2N-C_6H_4: 73%
R = 6-hydroxy-*n*-butyl, R' = 4-O_2N-C_6H_4: 59%
R = 2-pydidyl, R' = cyclohexyl: 87%
R = (2-phthalimidyl)ethyl, R' = perfluorophenyl: 80%

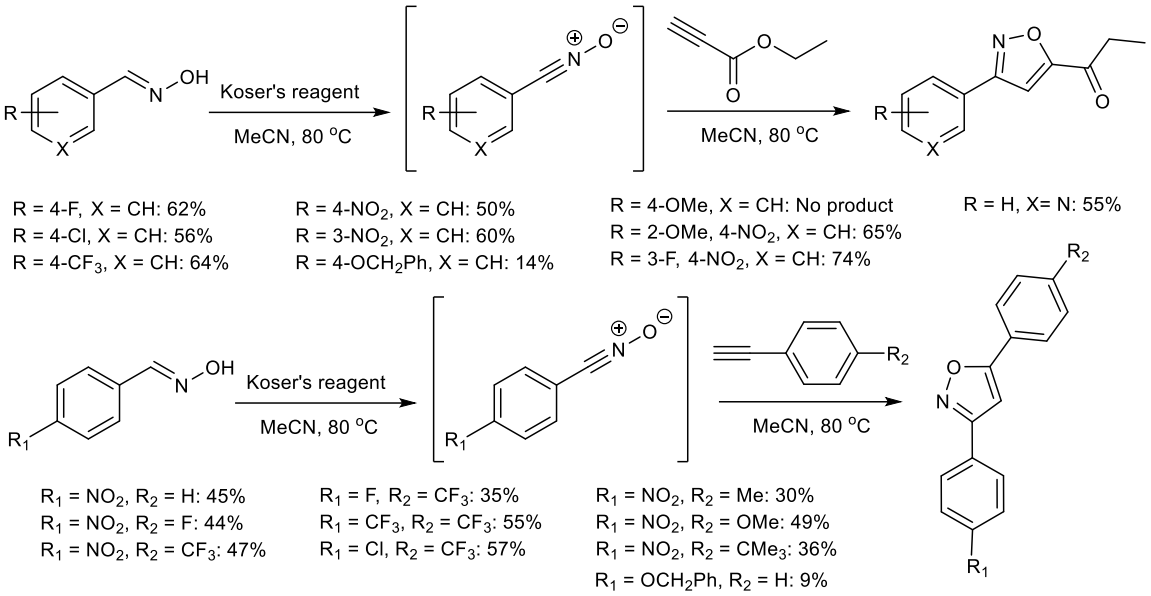
Scheme 14. The PIFA-induced cycloaddition of terminal alkynes and *in situ* nitrile oxides.[23]

This protocol was also feasible for the cycloaddition of nitrile oxides to unprotected nucleosides and peptides bearing terminal alkyne group. The reaction, therefore, was believed to be tolerable towards various sensitive functional groups (-OH and -NH_2).

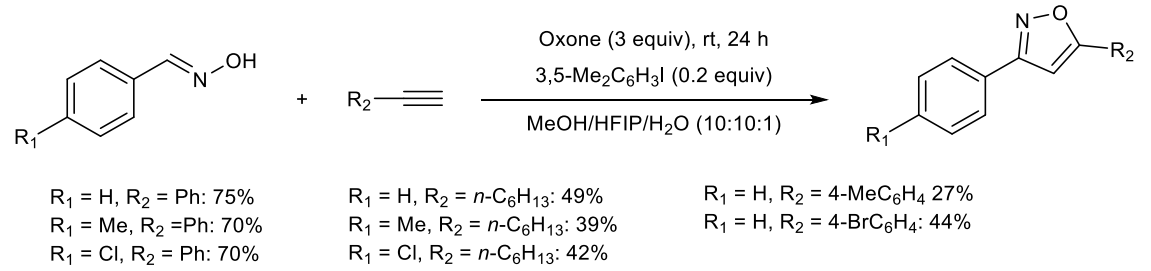
Koser's reagent was also studied for its activity in the cycloaddition of aromatic nitrile oxides to various alkynes. Although the reactions were carried out at an elevated temperature of 80 ^oC, only moderate yields of the corresponding isoxazoles were recorded for aldoximes bearing electron-withdrawing substituents. Meanwhile, weak reactivity was observed for the aldoximes bearing electron-donating substituents when no product or only negligible yields of desired isoxazoles were reported.[24]

Yoshimura *et al.* reported the cycloaddition of aromatic and aliphatic terminal alkynes to nitrile oxides generated by the action of hydroxy(aryl)iodonium ion under catalytic conditions. This activated hypervalent iodine species was generated *in situ* by

means of the reaction between an excess amount of oxone with a catalytic amount of 3,5-dimethyliodobenzene.[25]

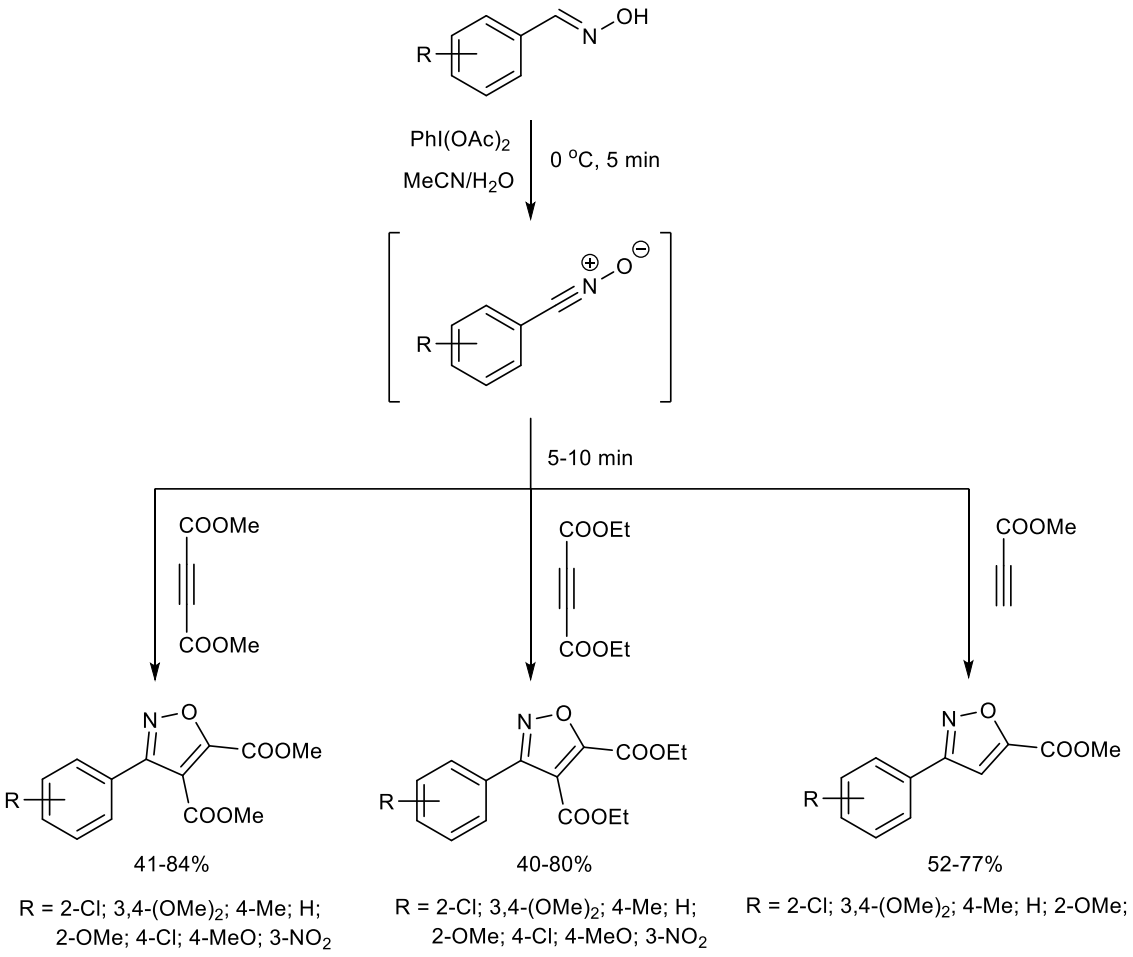


Scheme 15. Koser's reagent-mediated synthesis of substituted isoxazoles via cycloaddition of alkynes to nitrile oxides.[24]



Scheme 16. Catalytic cycloaddition of aldoximes to alkynes in the presence of *in situ* hypervalent iodine species.[25]

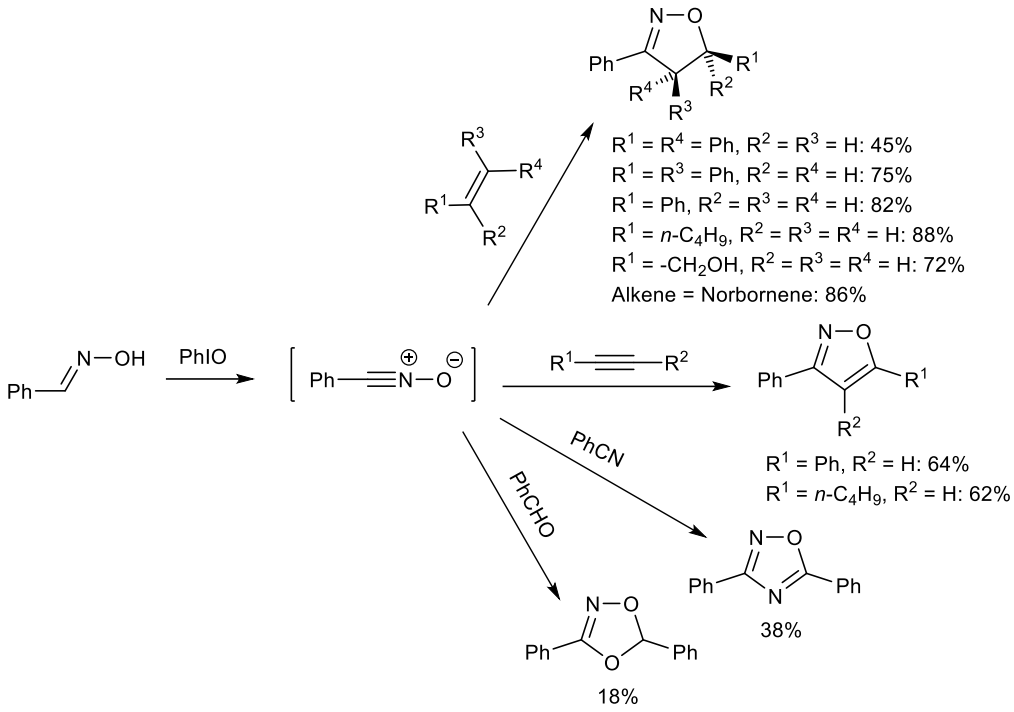
In 2016, Peddinti and co-workers developed a synthetic strategy of using oxidative reagent DIB to induce the formation of di- and tri-substituted isoxazoles via [3+2] cycloaddition of nitrile oxides to alkynes bearing electron-withdrawing groups. Various aromatic aldoximes including benzaldehyde oxime as well as its derivatives and 1-naphthaldehyde oxime were investigated for the reactivity towards cycloaddition with three different alkynes to afford 24 isoxazoles in total after 10-15 mins of stirring at 0 ^{o}C.[26]



Scheme 17. DIB-mediated formation of di- and tri-substituted isoxazoles via [3+2] cycloaddition of nitrile oxides.[26]

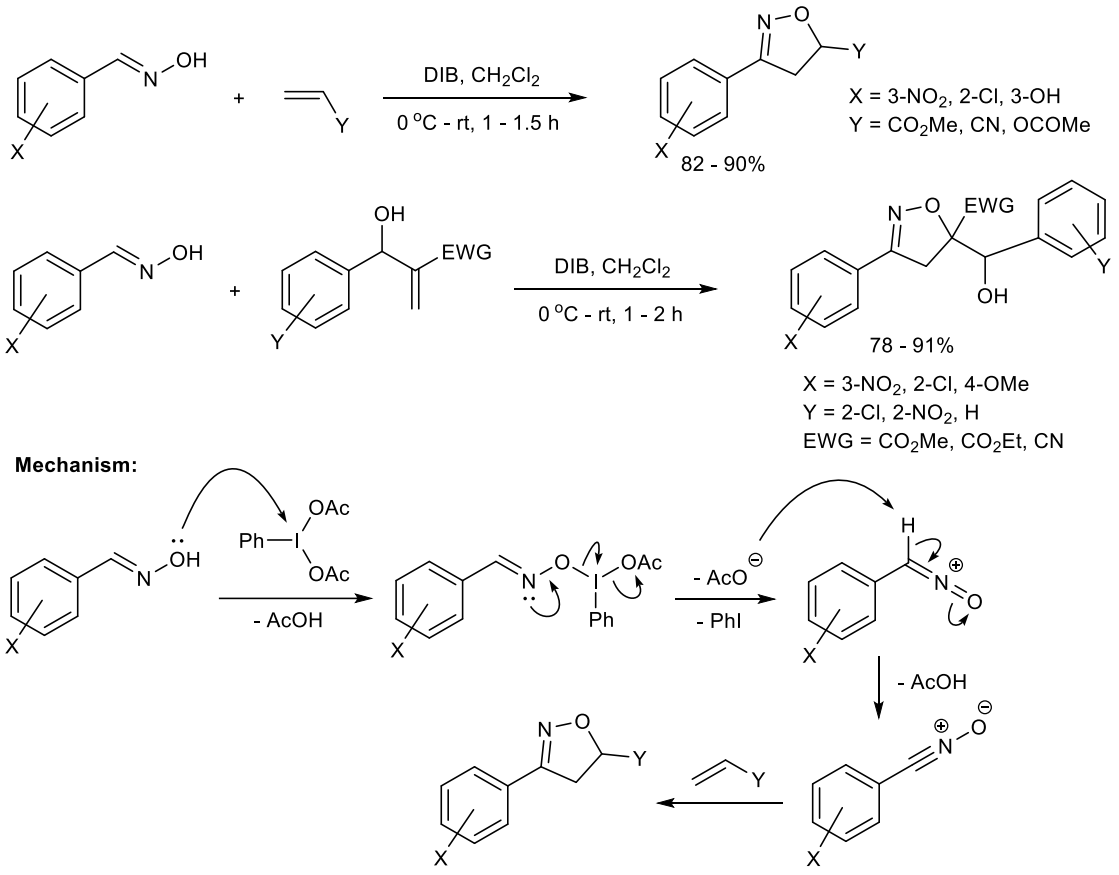
2.3.2.2.3. Cycloaddition with alkenes

The hypervalent iodine-mediated formation of isoxazolines as well as other heterocyclic compounds from aromatic aldoximes was first described by Takana and co-workers in 2002. In this research, iodosylbenzene (PhIO) was employed as an oxidative reagent to convert benzaldoxime in the presence of different dipolarophiles into corresponding oxidative cyclization products in fair to good yields for most cases. Without any trapping reagent, the nitrile oxide generated from benzaldoxime expectedly undergoes dimerization to give furoxan in almost quantitative yields.



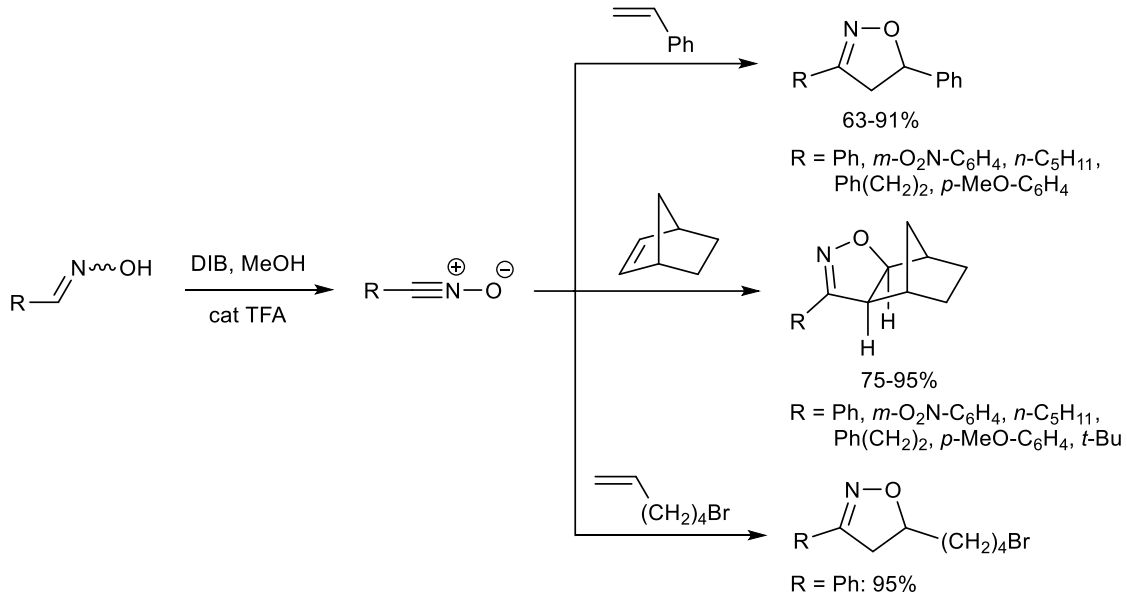
Scheme 18. Iodosylbenzene-mediated cyclization of benzaldoxime with different dipolarophiles.[27]

An alternative method to achieve the formation of isoxazolines from aromatic aldoximes and activated alkenes was then also reported by Reddy and co-workers in 2004. According to this procedure, an excess amount DIB was required to induce the quantitative *in situ* generation of nitrile oxides from aldoximes at mild conditions (0 ^{o}C - rt within 1 - 1.5 h). A consecutive cyclization step of reactive nitrile oxides with different activated olefins afforded various substituted isoxazolines in excellent isolated yields up to 90%. This method was also applicable for the preparation of isoxazolines derived from Baylis-Hillman adducts which are considered as important precursors to synthesize various bioactive compounds.[28]



Scheme 19. The reaction scope and mechanism of DIB-mediated formation of isoxazolines.[28]

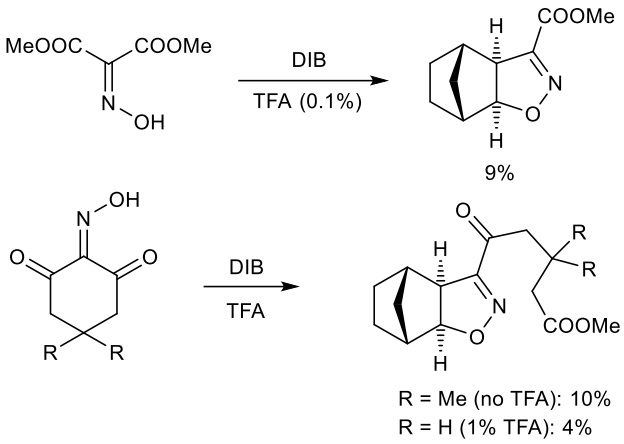
In 2009, Ciufolini *et al.* also reported the methodology to obtain substituted isoxazolines from aldoximes via the intermediate nitrile oxides generated in the presence of DIB. The optimization study was conducted in different solvents including $CHCl_3$, THF, TFE, HFIP, MeOH, and MeCN at room temperature. As the result, MeOH in combination with a small amount of TFA acting as an effective Brønsted acid promoter was the best solvent system. The reaction scope was investigated on both aromatic and aliphatic aldoximes with different trapping olefins to give various isoxazolines in good yields from 63 to 95%.[21]



Scheme 20. DIB-mediated cycloaddition of alkenes to nitrile oxides.[21]

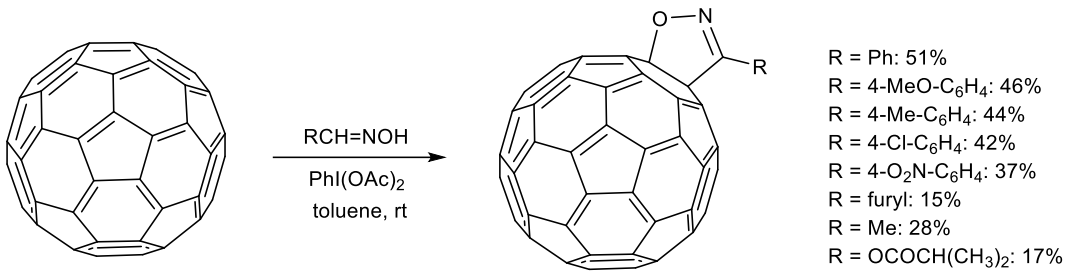
In another research published in 2011, Ciufolini and co-workers expanded the substrate scope to *α*-oxo-aldoximes and *α*-oxo-ketoximes for cycloaddition to alkenes. Each kind of oximes was oxidized in a different way by DIB to generate various nitrile oxides which were subsequently trapped with norbornene or styrene to form the final cycloadducts. The nitrile oxides deriving from *α*-oxo-ketoximes were obtained via the oxidative cleavage of the carbonyl-imino σ bond which simultaneously converted the carbonyl moieties into methyl ester groups under the presence of solvent methanol. Meanwhile, the carbonyl moieties in nitrile oxides generated from *α*-oxo-aldoximes were kept unchanged.[29]

The reactivity of *α,α'*-dioxo-ketoximes was also tested under the same reaction conditions. It was noted that the corresponding isoxazolines were formed in much lower yields than those deriving from mono-oxo homologues. It seemed likely that the presence of two carbonyl groups adjacent to the oxime group can diminish the nucleophilicity of the OH moiety by inductive and resonance electron-withdrawing effects as well as considerably prevent the OH group from cycloaddition to alkenes.[29]



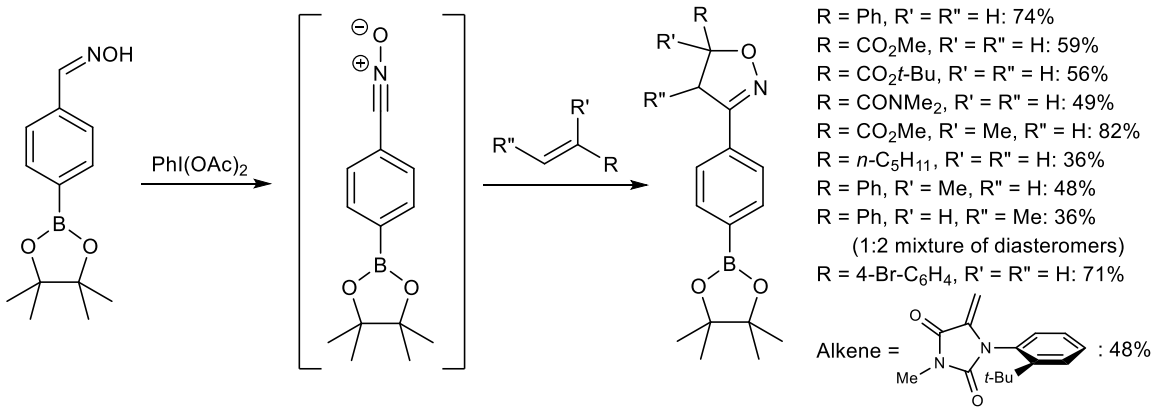
Scheme 21. DIB-mediated cycloaddition of poor substrates *α,α'*-dioxo-ketoximes.[29]

The oxidative performance of DIB on the dearomatization/cycloaddition of nitrile oxides to fullerene C_{60} was also studied. The cycloadducts, however, were only isolated in moderate yields (37-51%) in case of aromatic aldoximes. Even lower yields (15-28%) were observed for aliphatic or heterocyclic aldoximes.[30]



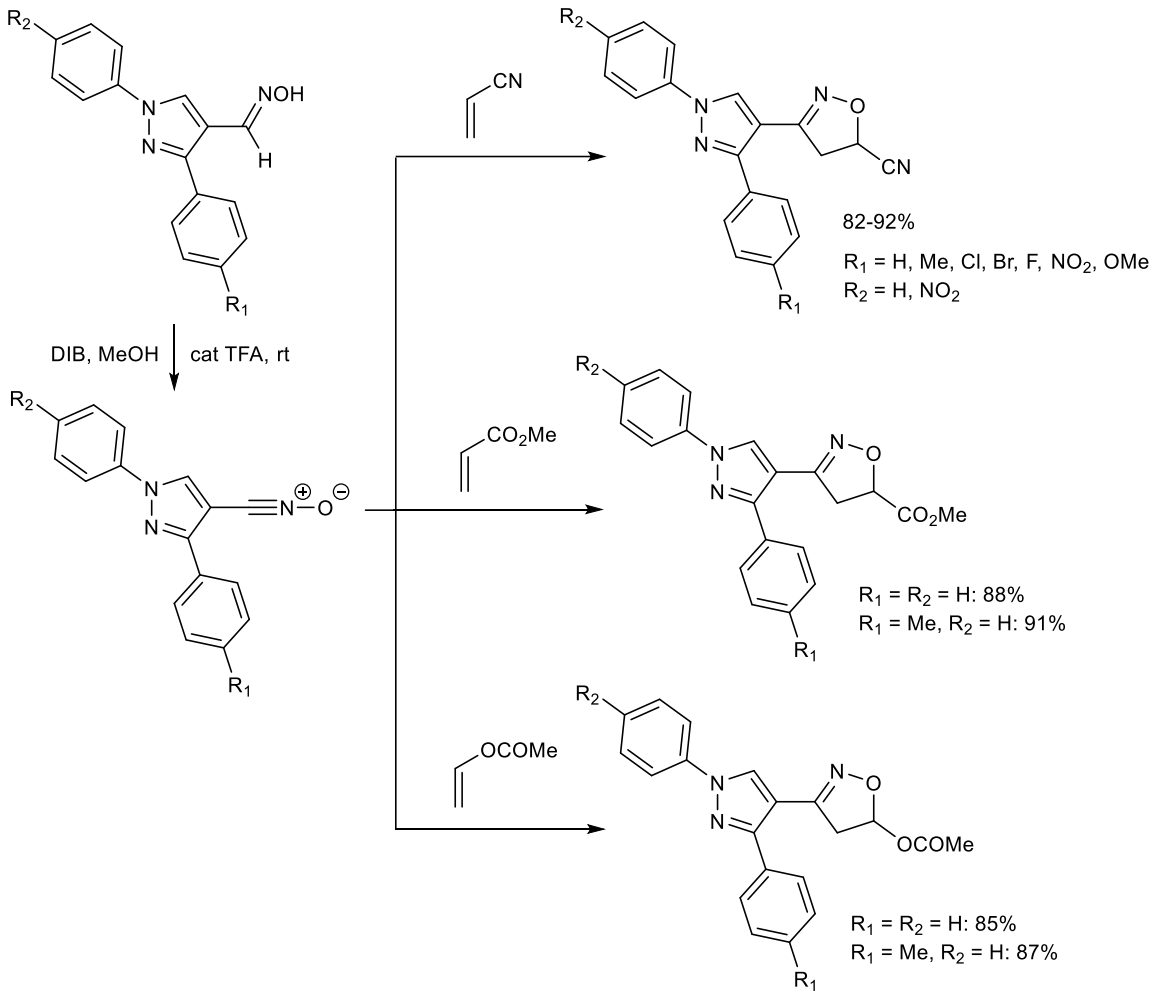
Scheme 22. DIB-mediated consecutive dearomatization/cycloaddition of nitrile oxides to fullerene C_{60}.[30]

In 2011, it was reported by Savage *et al.* that DIB exhibited a good tolerance towards aldoximes possessing boronate ester functional groups. The consecutive oxidation and cycloaddition were conducted at 0 ^{o}C in MeOH, to which a small amount (three drops) of TFA was added. All cycloadducts in which the boronate moieties were kept untouched were formed in varying yields ranging from 36% to 82%.[31]



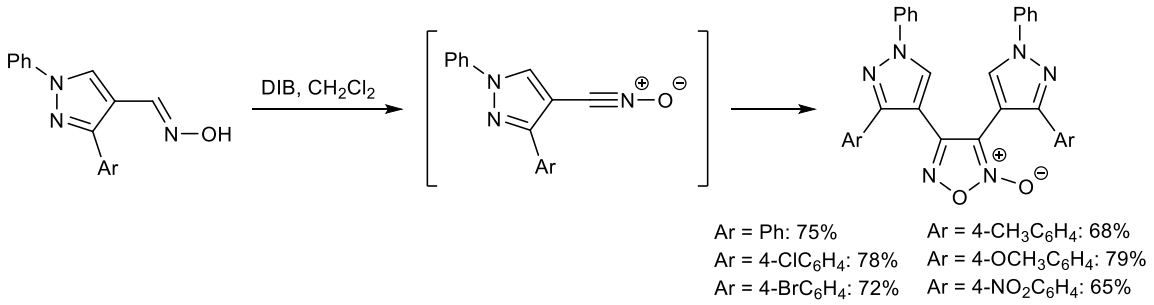
Scheme 23. Cycloaddition of 4-pinacolatoboron benzonitrile oxide with different alkenes.[31]

In previous publications, not much hypervalent iodine-mediated cycloaddition of heterocyclic aldoximes were reported. To fulfill this vacancy, Prakash's research group developed a procedure in which DIB was used as the oxidant to induce the cycloaddition of pyrazolyl aldoximes to activated alkenes bearing electron-withdrawing groups. All pyrazole-isoxazoline bis-heterocyclic compounds were obtained in high isolated yields from 82% to 92%.[32]



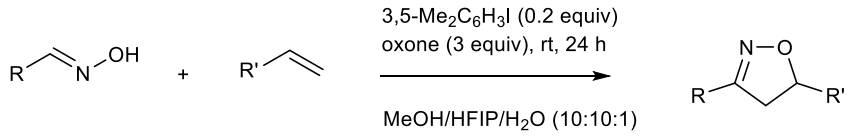
Scheme 24. DIB-mediated synthesis of pyrazolyl isoxazolines.[32]

In the absence of dipolarophiles, the nitrile oxides derived from pyrazolyl aldoximes easily underwent the dimerization to corresponding 3,4-bis(pyrazolyl)-1,2,5-oxadiazole-*N*-oxides in fair isolated yields (65-79%).[33]



Scheme 25. The DIB-mediated dimerization of pyrazolyl aldoximes.[33]

In 2013, Yoshimura *et al.* reported the efficacy of using *in situ* generated hydroxyl(phenyl)iodonium ion as the oxidant for the consecutive oxidation/cycloaddition of aldoximes with olefins. This activated hypervalent iodine species was obtained by the oxidation of corresponding iodobenzene by oxone. Interestingly, it was generated in a catalytic amount, consumed in the oxidation of aldoximes to release nitrile oxides, and then regenerated for the next catalytic cycles throughout the reaction time. From the optimization study, it was shown that the combination of 3,5-dimethyliodobenzene and oxone in the solvent system MeOH/HFIP/H_2O (10:10:1) gave the desired cycloadduct in the best yield. The reaction scope was studied for 11 olefins and 4 aldoximes under optimized conditions to prepare 16 different isoxazolines.[25]



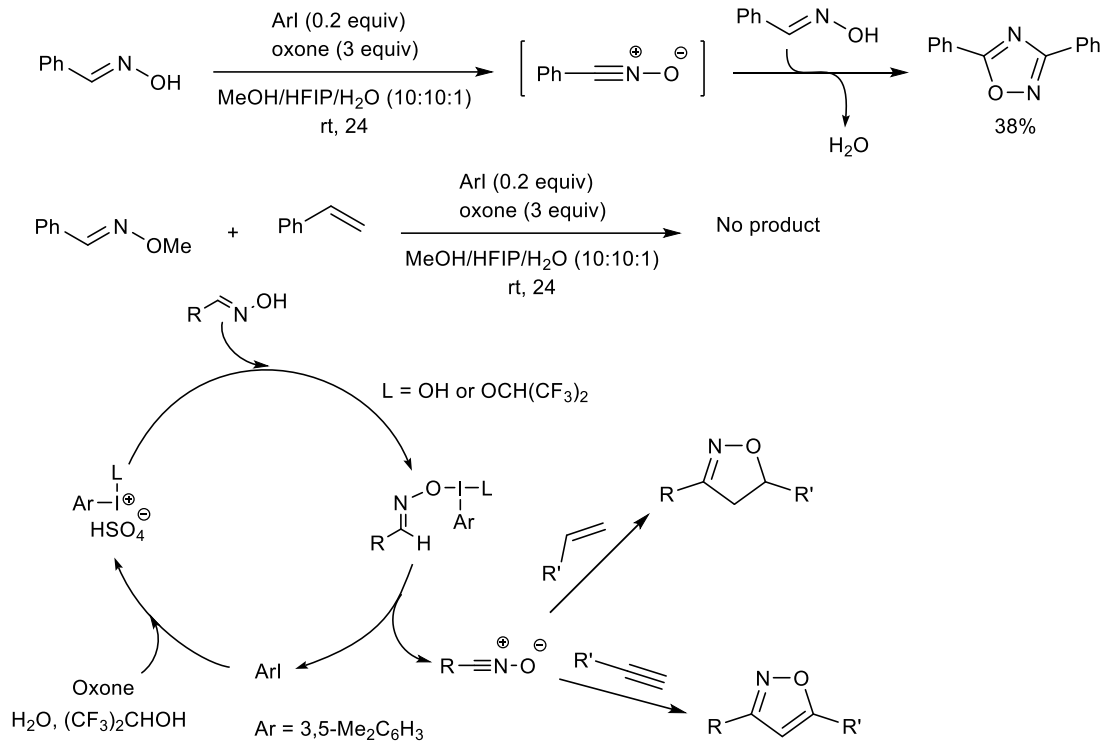
R = R' = Ph: 88%
R = Ph, R' = 4-Me-C_6H_4: 78%
R = Ph, R' = 3-Me-C_6H_4: 81%
R = Ph, R' = 4-Cl-C_6H_4: 92%
R = Ph, R' = 4-Br-C_6H_4: 87%

R = Ph, R' = 2-Br-C_6H_4: 89%
R = Ph, R' = 4-CF_3-C_6H_4: 99%
R = Ph, R' = CH_2Ph: 78%
R = Ph, R' = *n*-C_6H_{13}:69%
R = Ph, R' = *n*-C_8H_{17}: 71%

R = Ph, alkene = norbornene:30%
R = 4-Me-C_6H_4, R' = Ph: 71%
R = 4-Me-C_6H_4, R' = *n*-C_6H_{13}: 54%
R = 4-Cl-C_6H_4, R' = Ph: 77%
R = 4-Cl-C_6H_4, R' = *n*-C_6H_{13}: 79%
R = *n*-Pr, R' = Ph: 17%

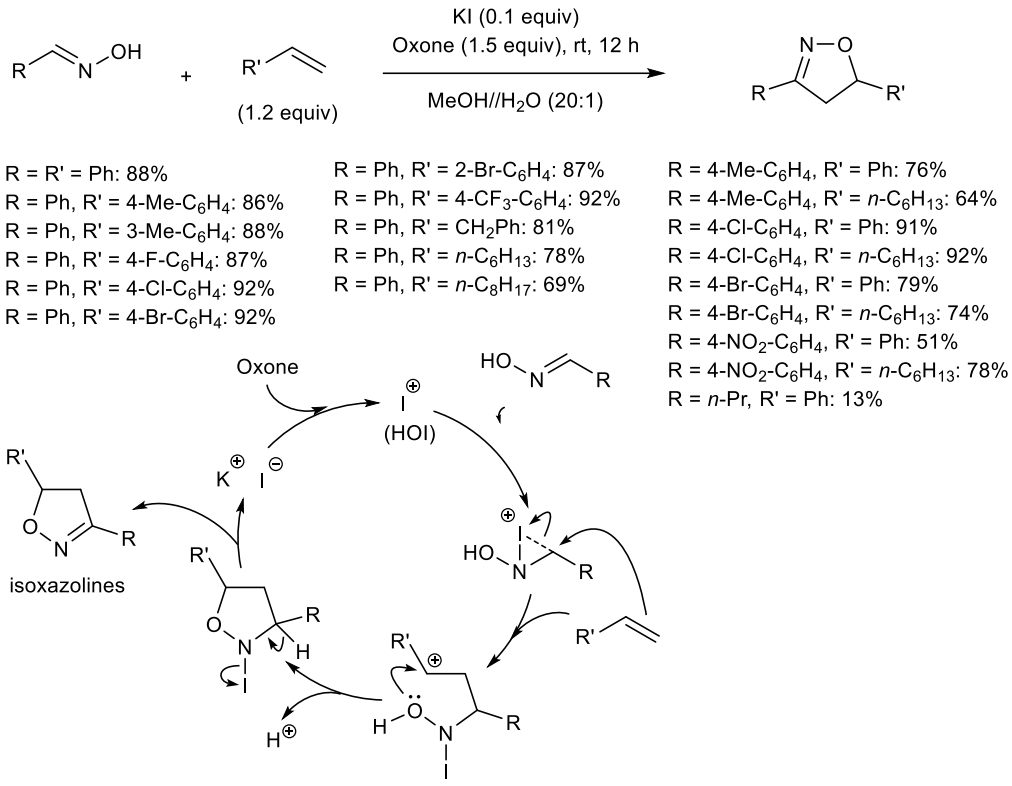
Scheme 26. Hypervalent iodine catalyzed cycloaddition of alkenes to nitrile oxides.[25]

The mechanism for the catalytic cycloaddition, as proposed in this paper, consisted of several consecutive steps, among which the ligand exchange between aldoximes and active hypervalent iodine species is required for the formation of nitrile oxides. Two control experiments were also performed to confirm the existence of ligand exchange step and nitrile oxide formation.[25]



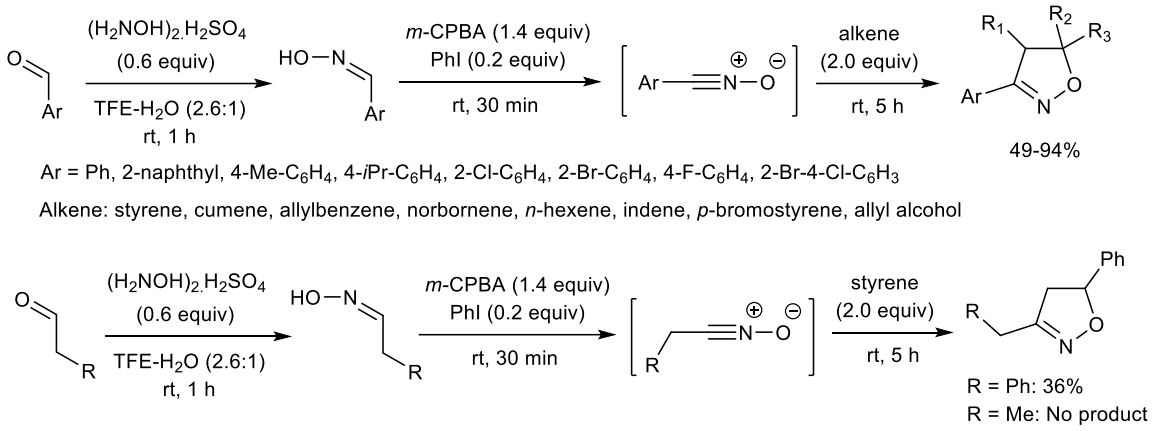
Scheme 27. Hypervalent iodine catalyzed cycloaddition of alkenes to nitrile oxides.[25]

Interestingly, as a part of the same research of consecutive oxidation/cycloaddition of aldoximes with olefins, Yoshimura and co-workers reported a more effective procedure in which KI, a cheap iodine source, instead of 3,5-dimethyliodobenzene was employed as the pre-catalyst whose loading was only 10 mol %. As expected, the investigated isoxazolines were formed in comparable yields to the analogues obtained in the procedure of using 3,5-dimethyliodobenzene as the pre-catalyst. Proposed mechanism showed that the reaction undergoes the formation of cyclic iodonium ylides instead of nitrile oxides as the reactive intermediates with the assistance of *in situ* generated hypoiodous acid.[34]

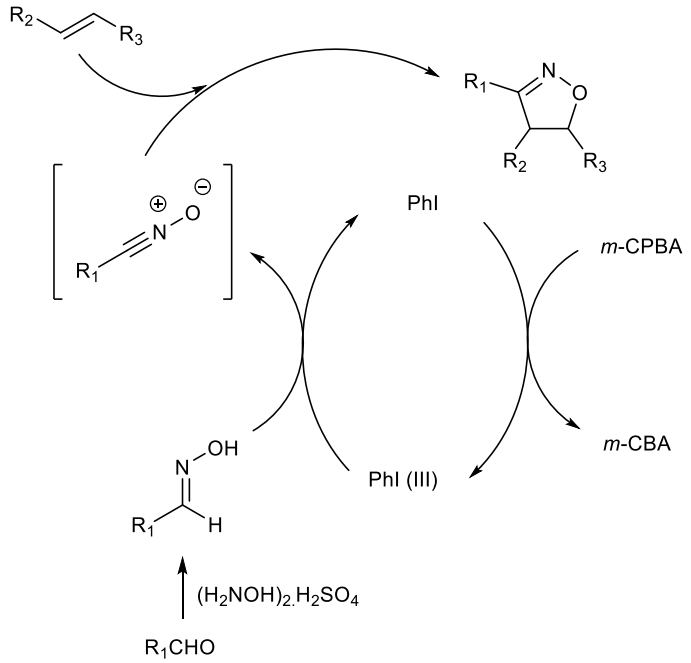


Scheme 28. The substrate scope and reaction mechanism of the KI-Oxone assisted formation of isoxazolines.[34]

Another catalytic protocol for the synthesis of isoxazolines from the cycloaddition of alkenes to nitrile oxides was developed by Yan's group in 2014. In their research, the active trivalent iodine species was generated *in situ* in catalytic amount from the oxidation of iodobenzene by *m*-CPBA. Remarkably, aldehydes instead of aldoximes were used as the starting materials to prepare isoxazolines following a convenient one-pot synthesis consisting of the preparation of aldoximes, oxidation of resulted aldoximes into nitrile oxides, and finally cycloaddition of nitrile oxides to alkenes. All investigated aromatic aldehydes reacted with various olefins to afford the desired isoxazolines in good yields for most cases. On the contrary, aliphatic aldehydes was significantly less reactive towards cycloaddition when a low yield of 36% was reported for the cycloadduct deriving from phenylacetaldehyde and no product was detected for propanal.[35]

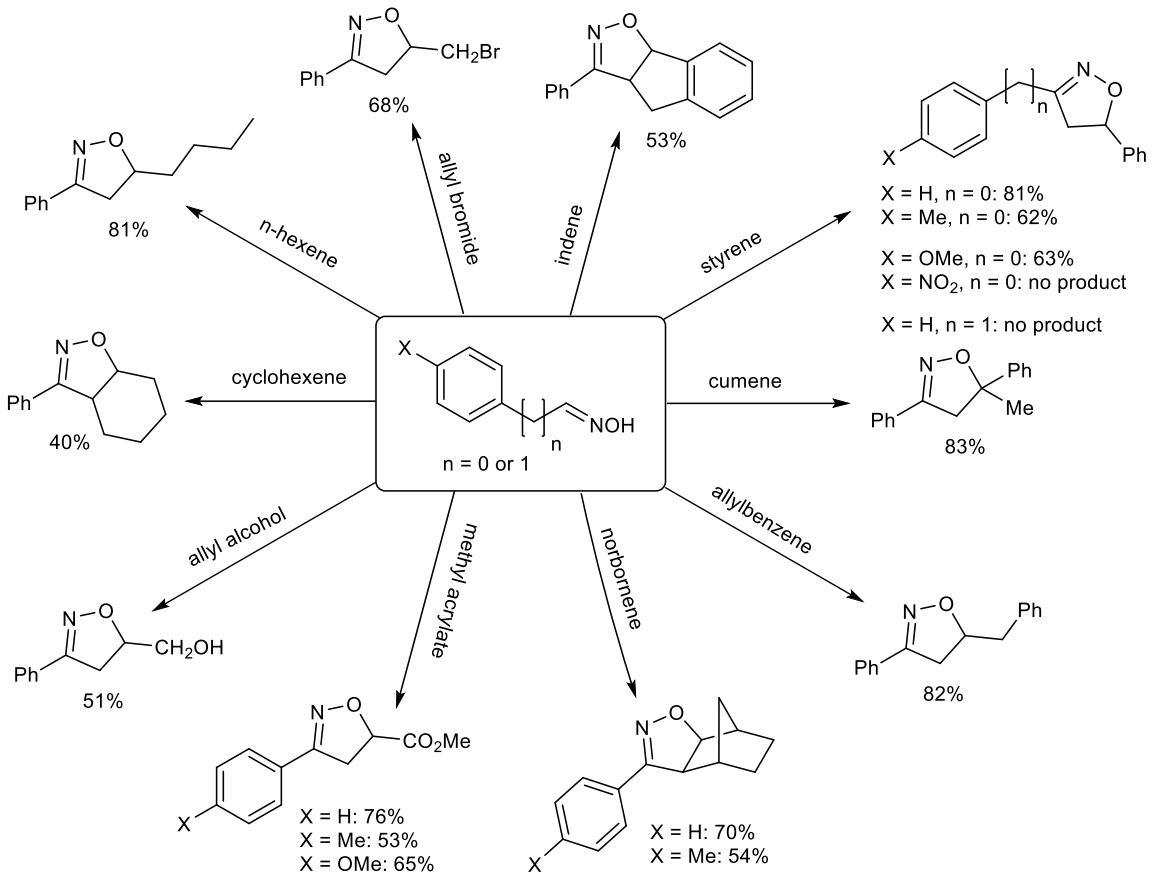


Scheme 29. One-pot synthesis of isoxazolines from aldehydes catalyzed by iodobenzene.[35]



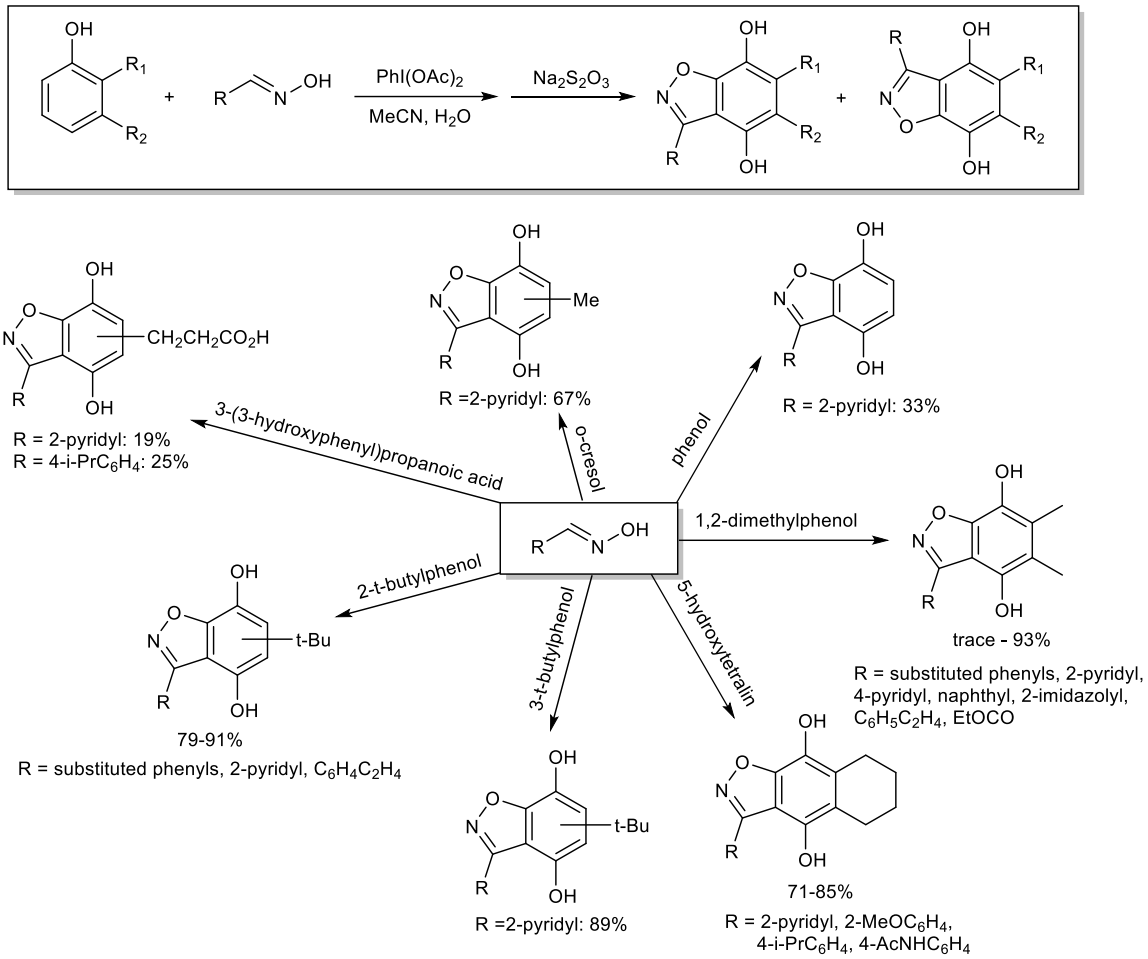
Scheme 30. Proposed mechanism for the iodobenzene-mediated one-pot synthesis of isoxazolines.[35]

In another publication in the same year, Yan and co-workers also reported a similar catalytic protocol in which aldoximes were used directly as the starting materials. The reaction scope was studied on the same olefinic reactants to give the same isoxazolines in similar isolated yields. Again, the poor reactivity of phenylacetaldoxime, an aliphatic aldoxime, towards cycloaddition was confirmed when no desired product was detected.[36]

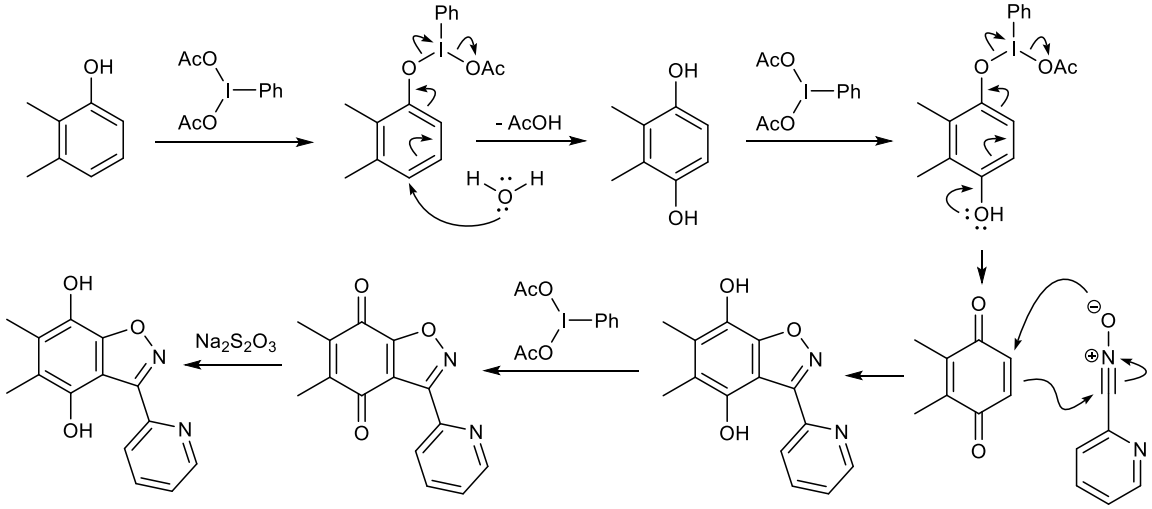


Scheme 31. Catalytic cyclization of aldoximes with alkenes under the assistance of *in situ* generated trivalent iodine species.[36]

The activity of DIB was also studied on the [3+2] cyclization for one-pot synthesis of benzo[*d*]isoxazole-4,7-diols in aqueous medium. As noted from the mechanism depicted in Scheme 32, the reaction goes through the *p*-benzoquinone adducts which was then converted to benzo[*d*]isoxazole-4,7-diols after the treatment with $Na_2S_2O_3$. The formation of two isomeric products can be observed for phenols bearing different substituents at *ortho*- and *meta*-positions ($R_1 \neq R_2$). Interestingly, the wide synthetic applicability of this reaction was also testified by the preparation of more complex molecules such as isoxazolo[5,4-*a*]phenazines, indazole-4,7-diols, and benzodiisoxazole-4,8-diols in moderate to fair isolated yields.[37]



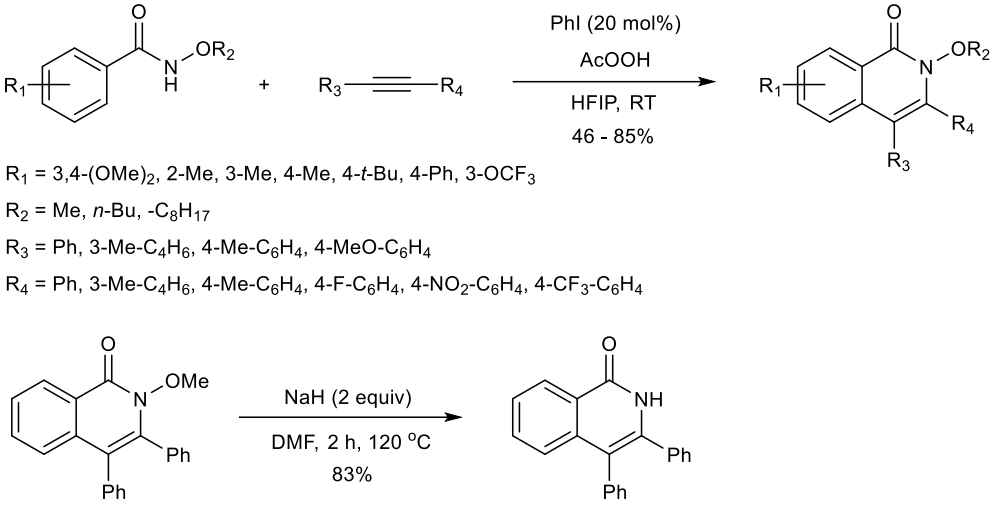
Scheme 32. The one-pot cyclization and reduction procedure for the synthesis of benzo[*d*]isoxazole-4,7-diols.[37]



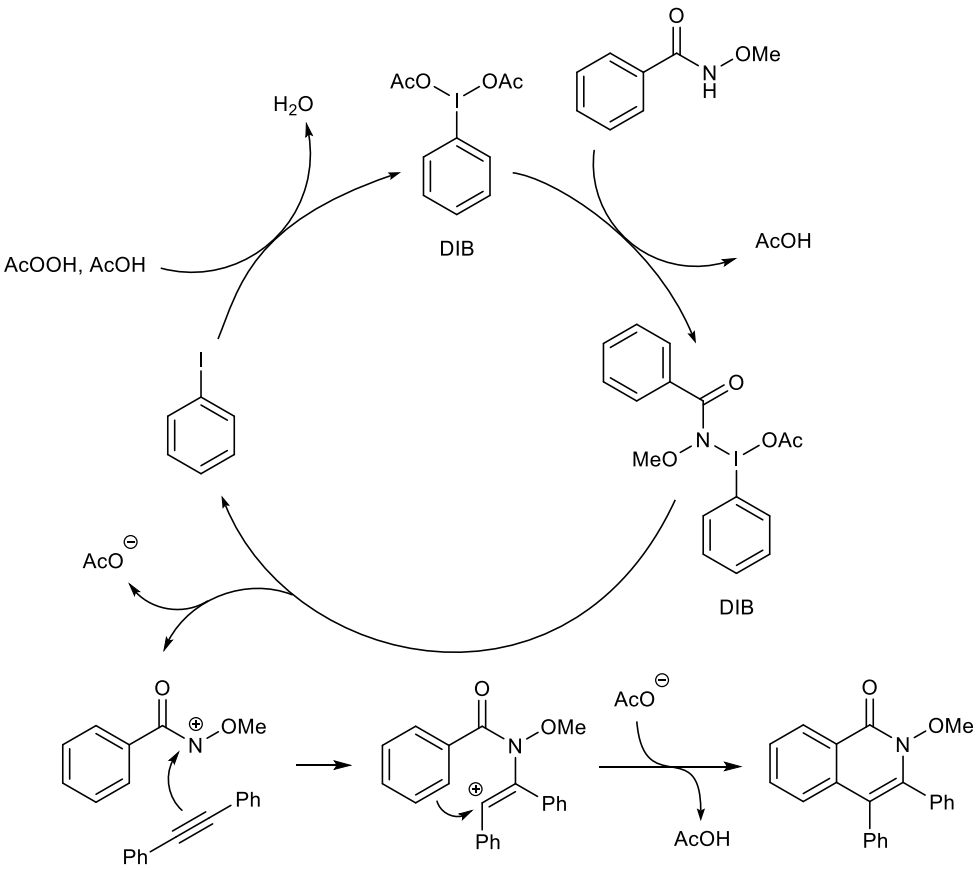
Scheme 33. The mechanism for DIB-assisted formation of benzo[*d*]isoxazole-4,7-diols.[37]

2.3.3. Other cycloadditions

In 2014, Antonchick and co-workers developed a transition metal-free method to achieve isoquinolones by the oxidative annulation of *N*-protected benzamide with alkynes. The reactions were performed under the catalysis of DIB generated *in situ* from iodobenzene and peracetic acid in solvent HFIP at room temperature to afford 19 *N*-protected isoquinolones in varying yields from 46% to 85%. A deprotection protocol of a typical cycloadduct was subsequently carried out to provide the desired isoquinolone with 83% yield.[38]

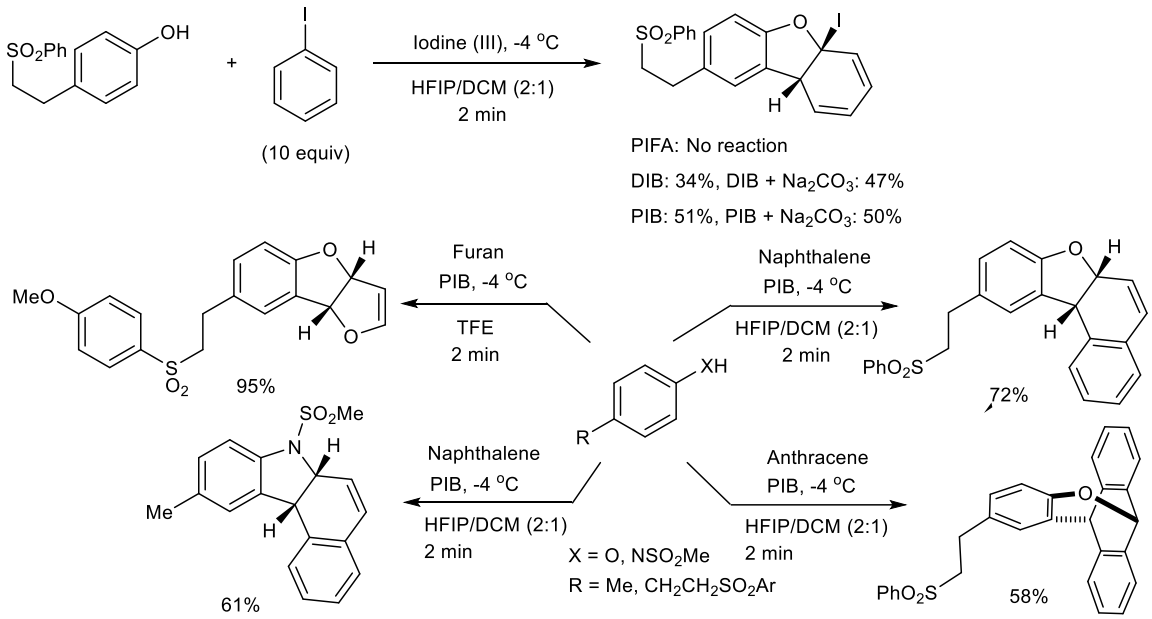


Scheme 34. The scope of the *in situ* DIB-catalyzed oxidative annulation.[38]

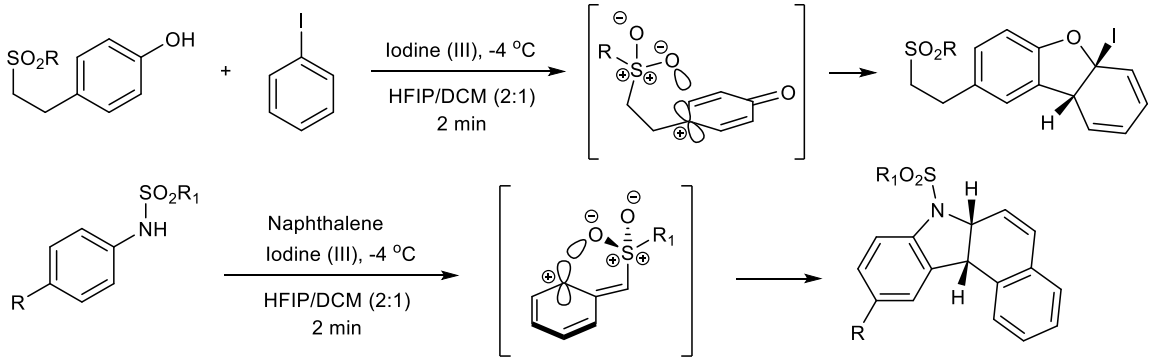


Scheme 35. Proposed mechanism of *in situ* DIB-catalyzed oxidative annulation of benzamide.[38]

The oxidative dearomatizing cycloaddition induced by different trivalent iodine compounds was studied by Canesi and co-workers in 2013 (Scheme 35). The use of polar and non-nucleophilic solvents such as HFIP and TFE as well as the presence of a sulfonyl moiety on the lateral chain of substrates was necessary to stabilize the electrophilic species generated during the hypervalent iodine-mediated umpolung activation (Scheme 36).[39]

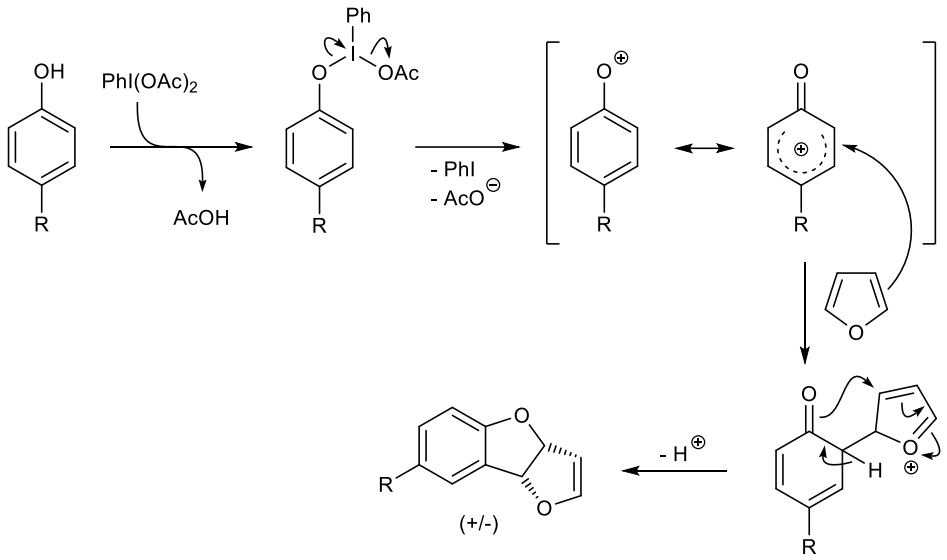


Scheme 36. Studies on optimization and substrate scope for iodine (III)-catalyzed oxidative dearomatizing cycloaddition.[39]

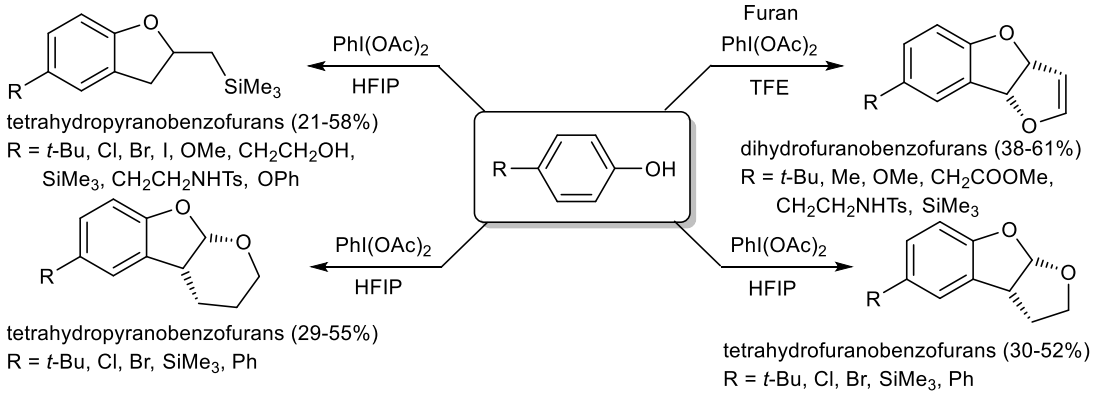


Scheme 37. Structures of electrophilic species generated by aromatic ring umpolung process[39]

Previously, Canesi *et al.* also reported the DIB-mediated cycloaddition of substituted phenols with sufficiently reactive alkenes to obtain various heterocyclic compounds such as dihydrofuranobenzofurans, tetrahydrofuranobenzofurans, tetrahydropyranopyranofurans, and dihyrobenzofurans (Scheme 37). Similar to the above oxidative dearomatizing cycloaddition, the hypervalent iodine catalyst induced an umpolung activation to convert an electron-rich substituted phenol to a reactive electrophilic intermediate which was subsequently attacked by an alkene to give the corresponding cycloadduct after consecutive steps (Scheme 38).[40]

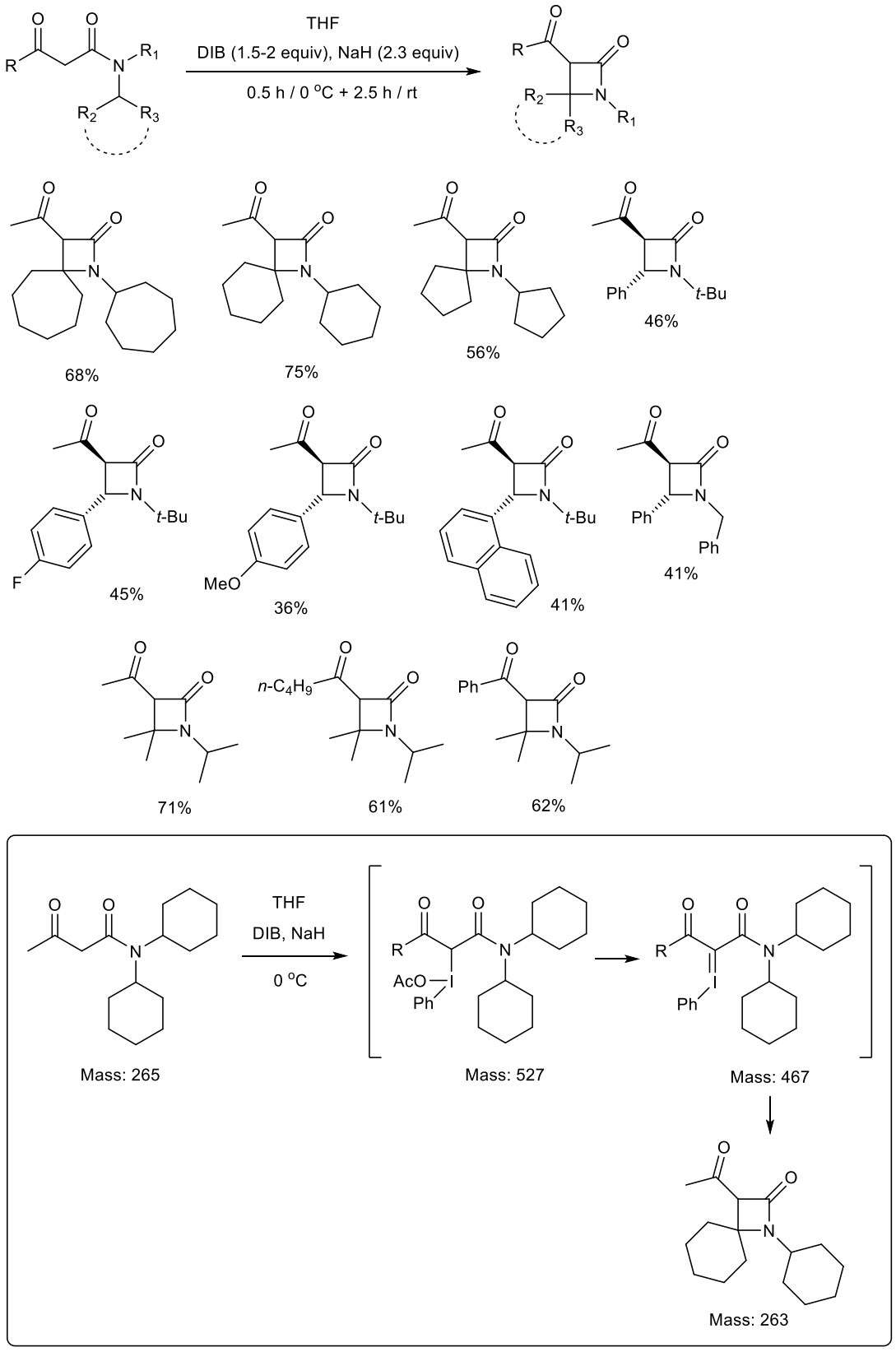


Scheme 38. Proposed mechanism of DIB-mediated cycloaddition of substituted phenol with furan.[40]



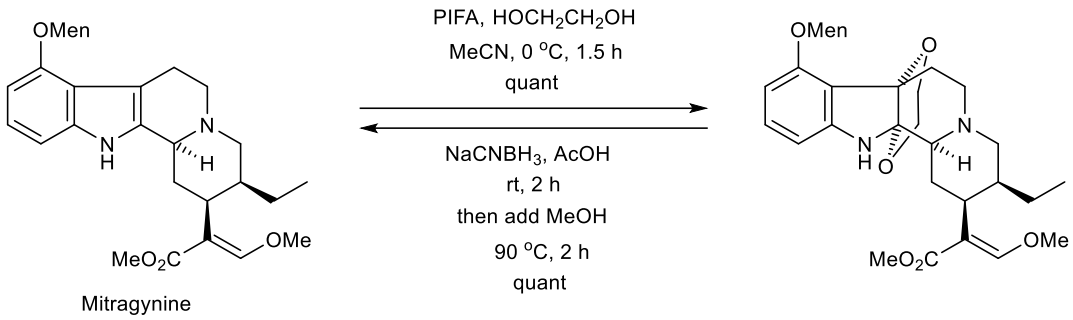
Scheme 39. Reaction scope of DIB-catalyzed cycloaddition of substituted phenols with different reactive alkenes.[40]

In 2015, Afonso and co-workers developed a DIB-catalyzed process to synthesize *β*-lactams in a single step which was much more convenient compared to the previous two-stepped process involving using transition metal catalysts and toxic, carcinogenic, and potentially explosive diazo compounds. The study on reaction mechanism by ESI-HRMS technique revealed the reaction undergoes the formation of intermediate iodonium ylides (mass: 467) which then intramolecularly cyclized to produce the corresponding products.[41]



Scheme 40. DIB-mediated synthesis of β-lactams via C-H insertion.[41]

As a part of an effort to prepare some potent antinociceptive analogues from mitragynine, a major constituent of *Mitragyna speciosa*, Takayama and co-workers developed an efficient method for protection-deprotection of 2,3-π bonds of indoles. The protecting process was performed under a mild condition (0 ^{o}C, 1.5 h) under the catalysis of PIFA to afford the 2,3-ethylene glycol bridged adducts in quantitative yields.[42, 43]

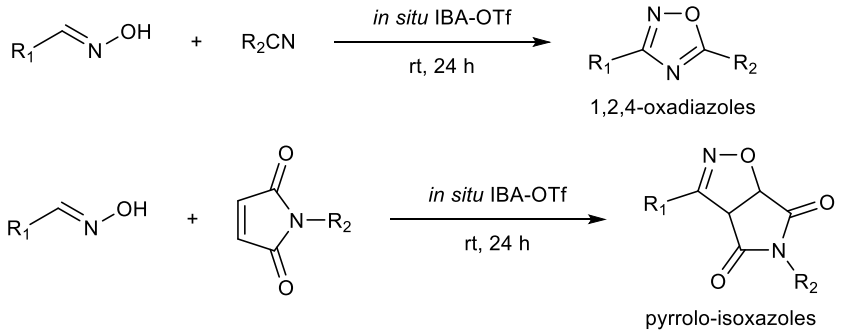


Scheme 41. The protection-deprotection of 2,3-π bonds of mitragynine.[42, 43]

3. RESULTS AND DISCUSSION

3.1. The aim of research

The aim of this research is to prepare some 1,2,4-oxadiazoles and pyrrolo-isoxazoles by the hypervalent iodine-mediated cycloaddition of *in situ* generated nitrile oxides to nitriles or maleimides. The hypervalent iodine species 2-[hydroxy(trifluoromethanesufonyloxy)]-iodobenzoic acid (IBA-OTf) was used in a catalytic amount to oxidize the starting material aldoximes into corresponding nitrile oxides. The cheap terminal oxidant *m*-CPBA and the additive TfOH acting as a ligand source were introduced to the reaction mixture in stoichiometric quantity to continuously transform a given monovalent iodine pre-catalyst 2-iodobenzoic acid into the active IBA-OTf in a catalytic cycle.



Scheme 42. IBA-OTf-mediated oxidative cyclization of aldoximes with nitriles and maleimides in catalytic condition.

3.2. Structural study and reaction scope of IBA-OTf

In previous research published in 2015, we reported the preparation, structural identification, and oxidative reactivity towards various organic substrates of IBA-OTf, a novel iodine (III) species, which is easily prepared from the 2-iodosylbenzoic acid (IBA) and TfOH.[44] The pseudocyclic square-planar structure of IBA-OTf was confirmed by X-ray crystallography showing the presence of two long weak bonds established by the intramolecular iodine–carbonyl oxygen interaction and intermolecular iodine–triflate oxygen (Figure 5). This structure provides a reasonable explanation for the increased thermal stability and solubility in common organic solvents of IBA-OTf compared to

IBA and iodosylbenzene. Further structural study of IBA-OTf by positive electrospray ionization mass spectrometry (ESI-MS) recorded in methanol demonstrated the presence of molecular cation $[C_6H_4CO_2HIOH]^+$ at *m/z* 265. Additionally, other cations generated from ligand-exchange reaction with methanol (*m/z* 279) and dimerization (*m/z* 525) were also observed in the ESI-MS spectrum.

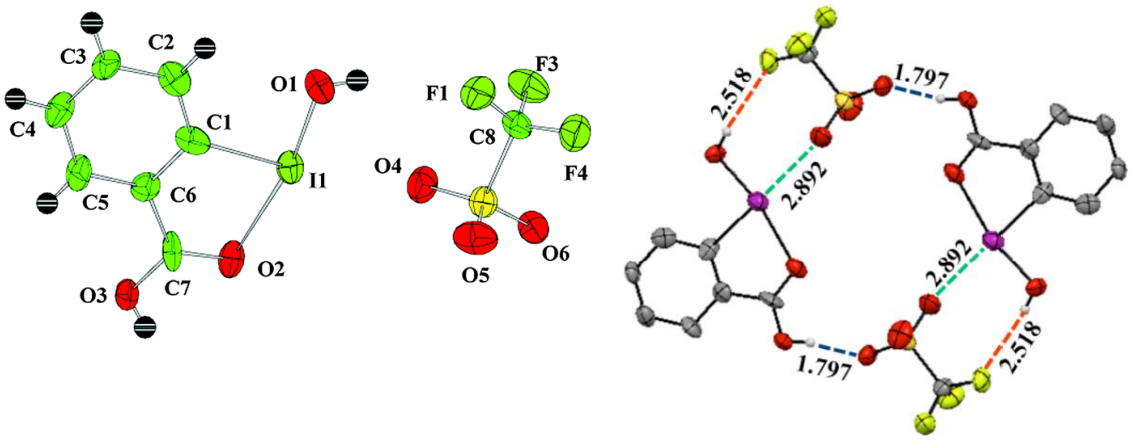


Figure 5. X-ray crystal structure of IBA-OTf and its intermolecular interaction in crystalline state.[44]

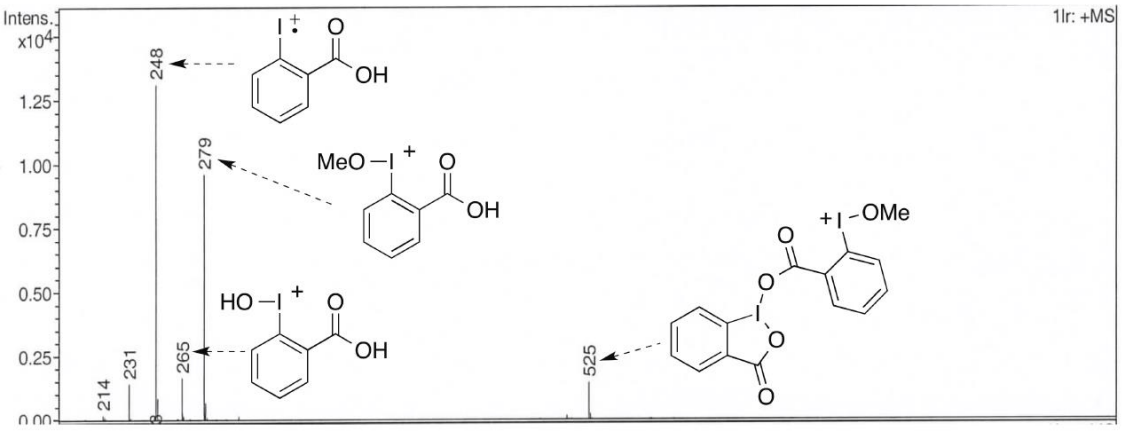
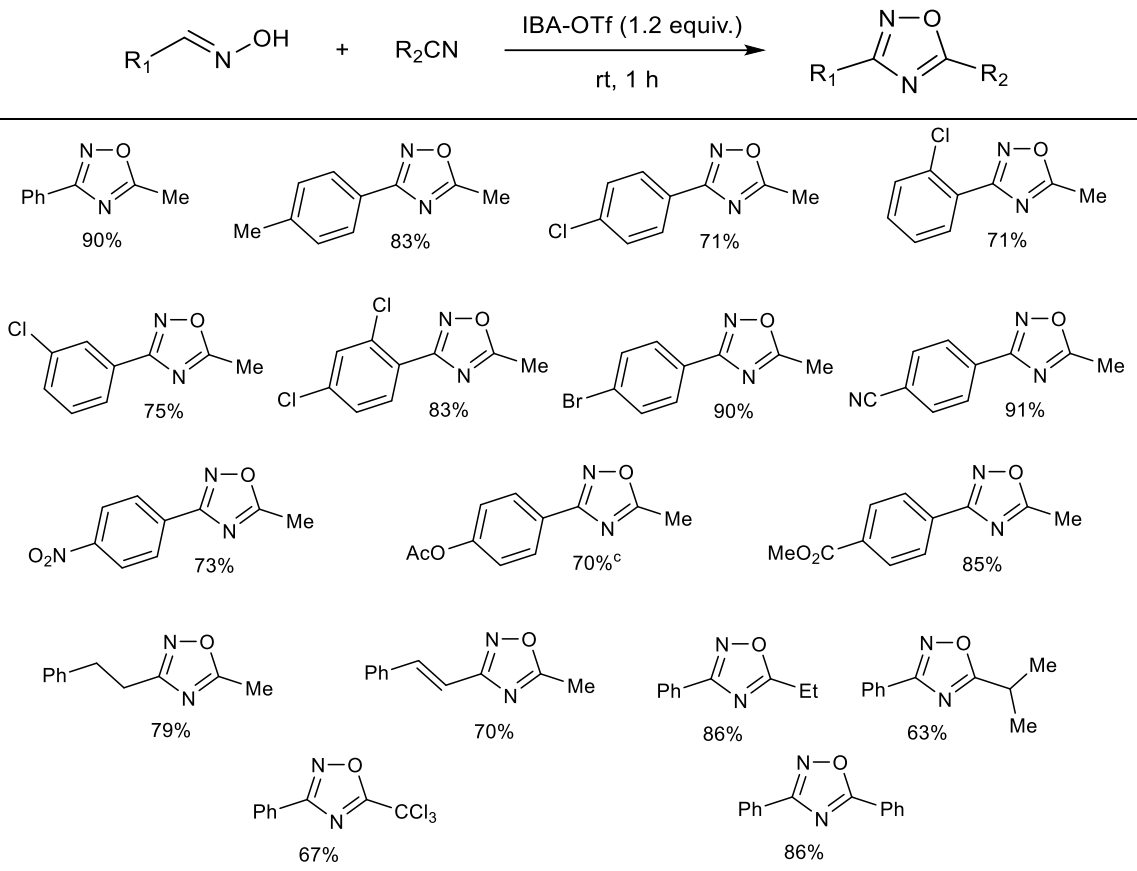


Figure 6. ESI-Mass spectrum of IBA-OTf in methanol solvent.[44]

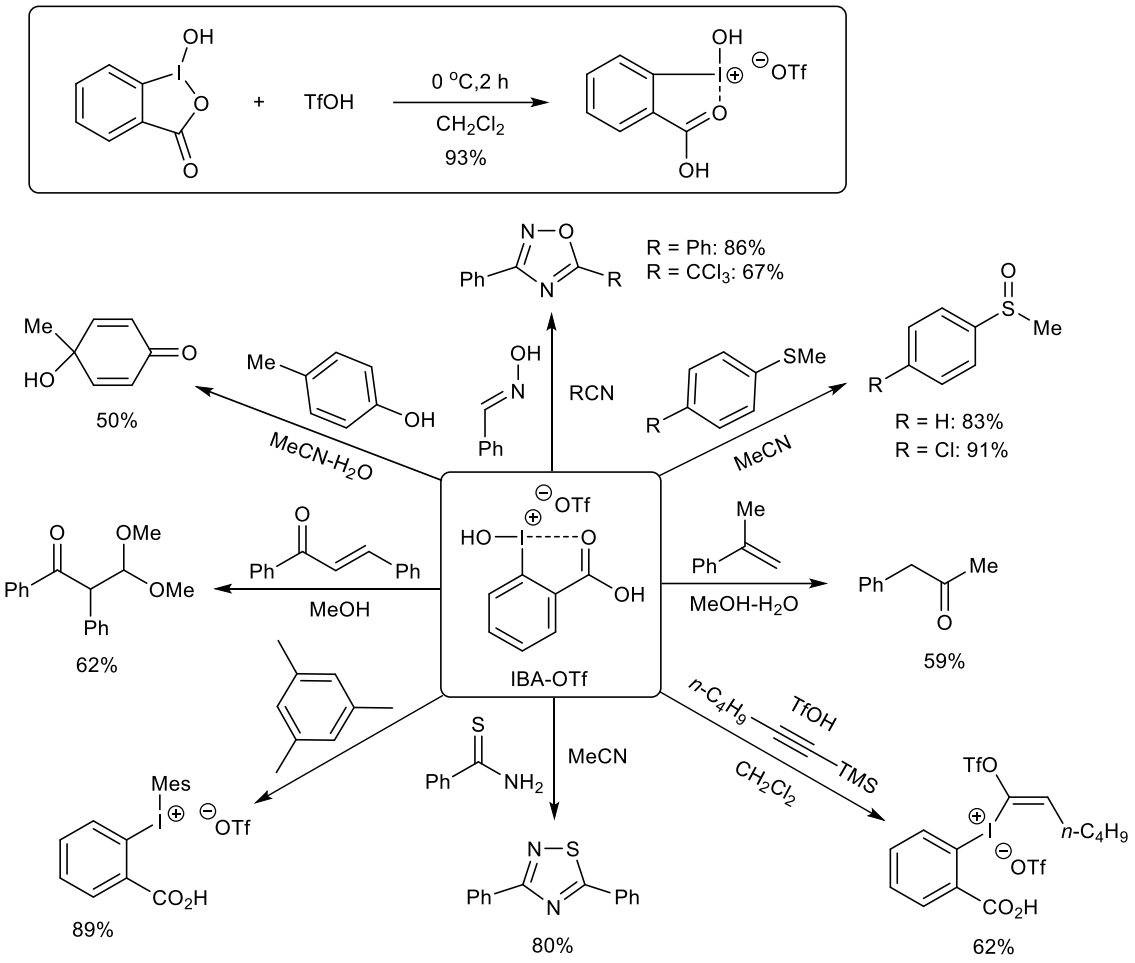
IBA-OTf was then tested for its oxidizing performance on a variety of organic substrates to afford the corresponding oxidatively functionalized products in moderate to good yields under mild conditions (Scheme 43). As expected, a stoichiometric amount of IBA-OTf (1-1.6 equiv) was required for a quantitative conversion. Further studies on

oxidative cyclization of different aldoximes with nitriles showed that this trivalent iodine species exhibited an excellent performance to induce the quantitative generation of corresponding nitrile oxides which then undergoes the cyclization with nitriles to give desired 1,2,4-oxadiazoles in good yields up to 91% (Table 1).[44] Such promising results encouraged us to develop a novel procedure for the synthesis of analogous oxadiazoles under catalytic conditions as presented in latter sections.

Table 1. Oxidative cycloaddition of aldoximes with nitriles using IBA-OTf.[a, b]



[a] Reagents and conditions: aldoximes (0.125 mmol) and IBA-OTf (0.15 mmol) in appropriate nitrile solvent (1 mL) at room temperature for 1 h. [b] Isolated yields. [c] Unprotected phenolic oxadiazole was also isolated in 9% as a by-product.



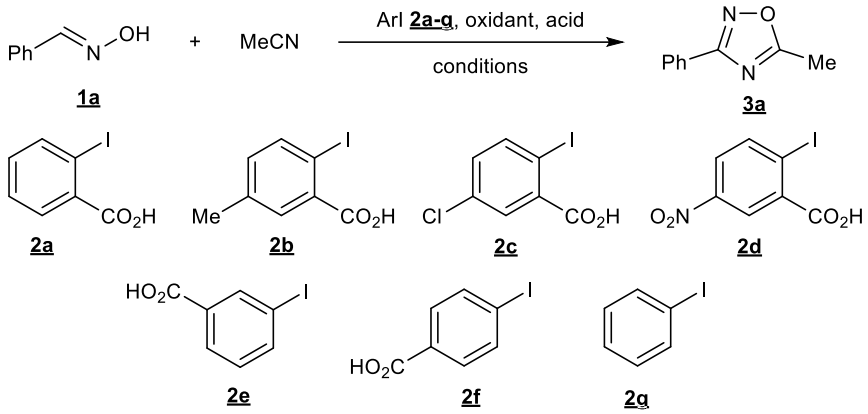
Scheme 43. The preparation and synthetic versatility of IBA-OTf in oxidative functionalization.[44]

3.3. IBA-OTf mediated formation of 1,2,4-oxadiazoles in catalytic condition

3.3.1. Optimization study

In the continuation of our research on the reactivity of IBA-OTf under catalytic conditions, we report herein the IBA-OTf-catalyzed formation of 1,2,4-oxadiazoles by the cycloaddition of aldoximes to nitriles. In this procedure, a cycle consisting of the generation of IBA-OTf from 2-iodobenzene in the presence of a terminal oxidant and TfOH and the oxidation of aldoximes by IBA-OTf to afford nitrile oxides and regenerate 2-iodobenzoic acid was repeated many times until all substrate was consumed. The *in situ* unstable nitrile oxides were then immediately captured by nitriles through 1,3-dipolar cycloaddition to produce desired 1,2,4-oxadiazoles.

Table 2. Optimization study for the hypervalent iodine-mediated cyclization of benzaldoxime with acetonitrile.



Entry	Temp. (°C), time (h)	ArI (equiv.)	Oxidant (equiv.)	Acid (equiv.)	**3a** (%)[a]
1	r.t., 24	**2a** (0.5)	*m*-CPBA (2.0)	TfOH (1.2)	86
2	r.t., 24	**2a** (0.5)	*m*-CPBA (2.0)	TfOH (none)	3
3	r.t., 24	**2a** (0.2)	*m*-CPBA (2.0)	TfOH (1.2)	86
4	r.t., 24	**2a** (0.1)	*m*-CPBA (2.0)	TfOH (1.2)	90
5	r.t., 24	**2a** (0.05)	*m*-CPBA (2.0)	TfOH (1.2)	86
6	r.t., 24	**2a** (0.025)	*m*-CPBA (2.0)	TfOH (1.2)	70
7	r.t., 24	**2a** (0.010)	*m*-CPBA (2.0)	TfOH (1.2)	76
8	r.t, 24	**2a** (none)	*m*-CPBA (2.0)	TfOH (1.2)	3
9	r.t., 24	**2a** (0.05)	*m*-CPBA (1.5)	TfOH (1.2)	86
10	r.t., 24	**2a** (0.05)	*m*-CPBA (1.2)	TfOH (1.2)	87 (83)
11[b]	r.t., 24	**2a** (0.05)	*m*-CPBA (1.2)	TfOH (1.2)	54
12	r.t., 6	**2a** (0.05)	*m*-CPBA (1.2)	TfOH (1.2)	76
13	r.t., 3	**2a** (0.05)	*m*-CPBA (1.2)	TfOH (1.2)	73
14	r.t., 1	**2a** (0.05)	*m*-CPBA (1.2)	TfOH (1.2)	44
15	r.t., 24	**2b** (0.05)	*m*-CPBA (1.2)	TfOH (1.2)	77
16	r.t., 24	**2c** (0.05)	*m*-CPBA (1.2)	TfOH (1.2)	81
17	r.t., 24	**2d** (0.05)	*m*-CPBA (1.2)	TfOH (1.2)	74
18	r.t., 24	**2e** (0.05)	*m*-CPBA (1.2)	TfOH (1.2)	81
19	r.t., 24	**2f** (0.05)	*m*-CPBA (1.2)	TfOH (1.2)	76
20	r.t., 24	**2g** (0.05)	*m*-CPBA (1.2)	TfOH (1.2)	73
21	r.t., 24	**2a** (0.05)	Oxone (1.2)	TfOH (1.2)	23

22	r.t., 24	**2a** (0.05)	70% TBHP (1.2)	TfOH (1.2)	1
23	r.t., 24	**2a** (0.05)	30% H_2O_2 (1.2)	TfOH (1.2)	1
24	r.t., 24	**2a** (0.05)	*m*-CPBA (1.2)	H_2SO_4 (1.2)	10
25	r.t., 24	**2a** (0.05)	*m*-CPBA (1.2)	*p*-TsOH (1.2)	6
26	r.t., 24	**2a** (0.05)	*m*-CPBA (1.2)	TFA (1.2)	3
27	r.t., 24	**2a** (0.05)	*m*-CPBA (1.2)	AcOH (1.2)	7

[a] Yields are calculated from ^{1}H NMR spectra of reaction mixtures using 1,1,2,2-tetrachloroethane as internal standard (numbers in parentheses are reported as isolated yields). [b] Dichloromethane solution of 10 equivalents of MeCN was employed instead of MeCN solvent.

First, optimization studies were conducted on the model reaction between benzaldoxime **1a** and acetonitrile. It can be seen from the Table 2 that at least 5 mol% of **2a** was required for a quantitative transformation to furnish the desired product **3a** in the best yields from 86 to 90% (entry 1, 3-5). Only a trace amount of **3a** (3%) was detected while 83% of starting material **1a** was recovered when the reaction was performed in the absence of iodine resource **2a** (entry 8).

Reducing the quantity of *m*-CPBA down to 1.2 equiv. did not result in any variation in the yield of **3a** (entry 5, 9, and 10). This result is in agreement with the proposed mechanism in which only an equivalent amount of terminal oxidant is expected to be sufficient for a complete conversion of aldoximes into corresponding nitrile oxides. The reaction was then performed in dichloromethane solution containing 10 equiv. of MeCN to give **3a** in a moderate yield of 54% (entry 11) which is much lower than those carried out in MeCN as a solvent. Decreasing the reaction time from 24 h to 1 h while keeping other experimental parameters constant reduced the yield of **3a** from 87% to 44% (entry 10 and 14). Varying the reaction time within the interval from 3h to 6 h did not lead to any significant change in reaction yield (entry 12 and 13).

A study on the structure-reactivity relationship of iodoarenes revealed that except **2a** exhibiting the unusual pre-catalytic activity to produce **3a**, there was no much difference in reactivity for the remaining iodoarenes **2b-g** (entry 15-20). The reactivity of other terminal oxidants was also investigated, and the results showed that except a low yield of

3a (23%, entry 21) observed for oxone, only trace amounts of **3a** (1%, entry 22 and 23) were obtained in the presence of TBHP or H_2O_2. In a similar way, replacing TfOH by other acidic ligands including H_2SO_4, *p*-TsOH, TFA, and AcOH resulted in the negligible formation of **3a** with the NMR yields ranging from 3% to 10%. Generally, it can be easily concluded that the reaction was partially controlled by the acidity of the ligands when TfOH which is about 1000 times stronger than H_2SO_4 afforded the cycloadduct **3a** in much higher yield than other acidic ligands. However, unfortunately, for the rest of investigated acidic ligands, it is hard to make a comparison on their reactivity due to a minor difference in yield of **3a** (entry 24-27).

3.3.2. Substrate scope study

The optimized conditions were then applied for the preparation of a variety of substituted 1,2,4-oxadiazoles, and the results are presented in Table 3. In general, under appropriate conditions, the substrates bearing either electron-withdrawing or electron-donating substituents can effectively react with nitriles to form the corresponding 1,2,4-oxadiazoles in good isolated yields. However, for those containing strongly electron-withdrawing groups such as **1h**, **1i**, and **1k**, a slight decrease in isolated yields of corresponding substituted 1,2,4-oxadiazoles was recorded. These results will make sense if the effect of substituents on the contribution of different resonance structures of nitrile oxides is taken into consideration.

It is commonly known that nitrile oxides are represented in five resonance forms among which A and B are those whose contributions are the most notable (Figure 7). We believe that the cycloaddition of nitrile oxides with a typical asymmetric dipolarophile like acetonitrile can be more favored if the resonance structure A is involved in the concerted pericyclic cycloaddition step. In this transition state, it is easy for acetonitrile to approach towards nitrile oxides in the manner in which the electrostatic interaction between the dipole of acetonitrile and nitrile oxides is reinforced. On the other hand, the nucleophilic attack of acetonitrile to the resonance form B is not favored due to the repulsive electrostatic force between the dipole of acetonitrile and nitrile oxides (Figure 8). The contribution of resonance structure B, in turn, is more significant for nitrile oxides generated from aldoximes bearing strongly electron-withdrawing groups such as -

CN (**1h**), -NO_2 (**1i**), and -CO_2Me (**1k**) which can effectively delocalize the negative charge on carbon center by resonance effect. As a result, their reactivity in pericyclic addition with acetonitrile is diminished due to the lessening contribution of resonance structure A and a drop of about 10% in isolated yield was observed for these substrates.

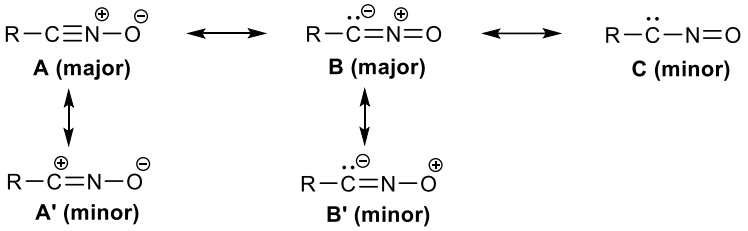


Figure 7. Different resonance structures of nitrile oxides.

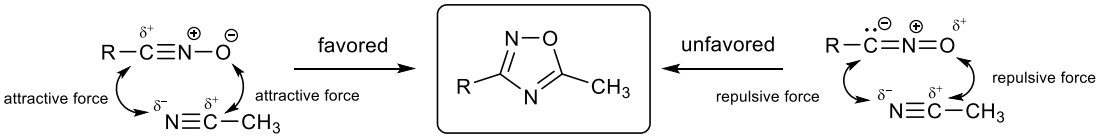
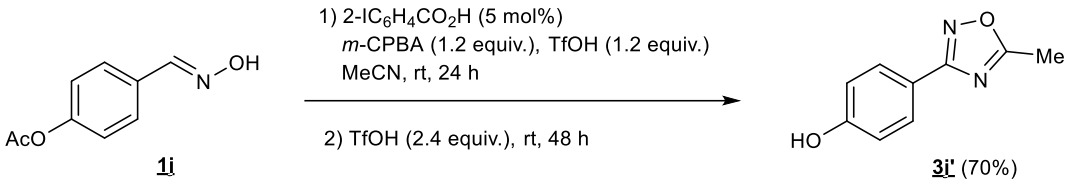


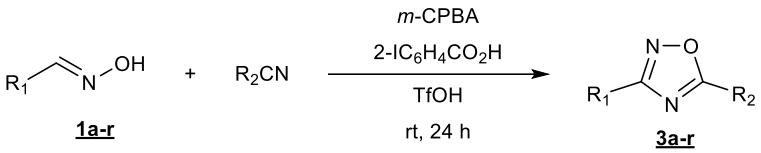
Figure 8. Proposed electrostatic interaction in the transition states of the pericyclic cycloaddition between nitrile oxide and acetonitrile.

The cycloadditions of nitrile oximes derived from typical aliphatic or *α,β*-unsaturated aldoximes, hydrocinnamaldehyde oxime **1l** and cinnamaldehyde oxime **1m**, respectively, with acetonitrile afforded the corresponding products in moderate yields. For the starting material **1j** bearing a susceptible acetoxy substituent, the deacylated phenolic oxadiazole **3j'** instead of the expected one **3j** was formed in the majority with an isolated yield of 56%. Further stirring of the reaction mixture in the presence of an additional amount of TfOH for 48 h resulted in the formation of **3j'** as the only product in 70% isolated yield. Interestingly, a trivially modified procedure where the amounts of *m*-CPBA and TfOH were both adjusted to 3 equivalents with respect to the substrate terephthalaldehyde dioxime **1n** was successfully employed to prepare dicycloadduct **3n** in a good isolated yield of 88%.



Scheme 44. One-pot synthesis of phenolic oxadiazole.

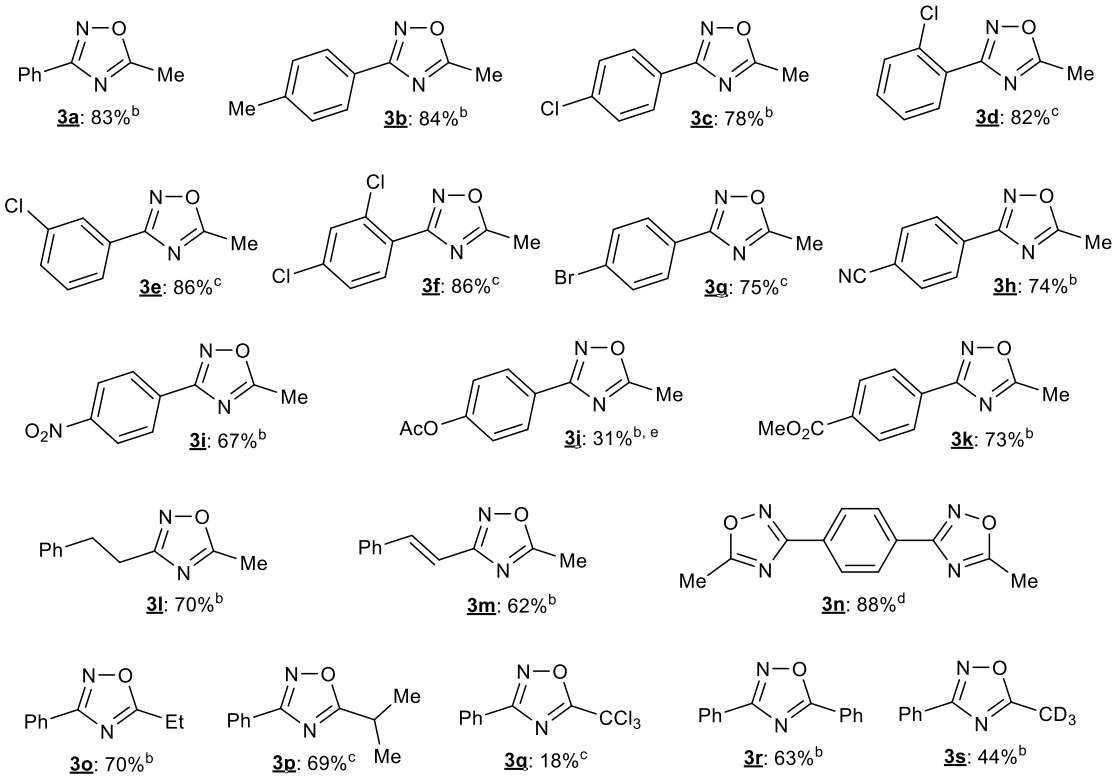
Table 3. Study on reactant scope of oxidative cyclization of aldoximes with nitriles using catalytic IBA-OTf.[a]



[b]Method A: 2-$IC_6H_4CO_2H$ (5 mol%), TfOH (1.2 equiv.), *m*-CPBA (1.2 equiv.)

[c]Method B: 2-$IC_6H_4CO_2H$ (10 mol%), TfOH (1.2 equiv.), *m*-CPBA (1.5 equiv.)

[d]Method C: 2-$IC_6H_4CO_2H$ (5 mol%), TfOH (3.0 equiv.), *m*-CPBA (3.0 equiv.)



[a] Isolated yields. [e] The corresponding deacylated phenolic **3j'** was also isolated in 56% yield.

We then investigated the reaction scope of various nitriles bearing different substituents such as ethyl (**1o**), isopropyl (**1p**), trichloromethyl (**1q**), and phenyl (**1r**). At first glance, it seemed that this cycloaddition was apparently governed by the electronic effects of nitriles when the presence of a typical electron withdrawing substituent such as trichloromethyl drastically reduced the isolated yield of corresponding product **3q** down to 18%. However, it should be known from the viewpoint of frontier molecular orbital theory (FMO) that both electron-rich and electron-poor dipolarophiles can accelerate the reaction to give the desired cycloadducts in high yields. According to this theory, the 1,3-cycloaddition of nitrile oxides is classified in type II where the bond formation in transition states can be achieved by one of two following mechanisms: i) the overlap between the HOMO of dipolarophile and the LUMO of nitrile oxide; ii) the overlap between the LUMO of dipolarophile and the HOMO of nitrile oxide (Figure 9). For a given dipolarophile, it is known that an electron-withdrawing group would lower the energy of MOs while an electron-donating group would raise the energy of MOs in the dipolarophile. The energy gap between two interacting MOs in dipole (nitrile oxide) and dipolarophile (nitrile) therefore is reduced in both cases, accounting for the increasing reactivity observed for both electron-rich and electron-poor dipolarophiles. The steric effect of trichloromethyl moiety should be taken into consideration to explain the exceptional poor yield of **3q**.

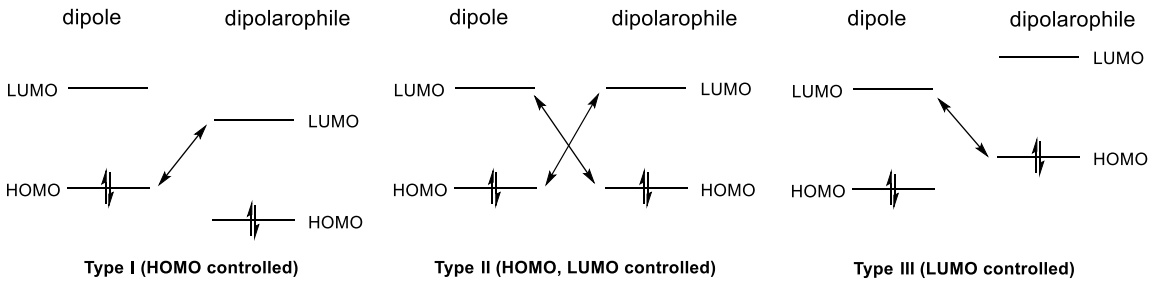


Figure 9. Sustmann's classification of 1,3-dipolar cycloadditions.

3.3.3. Studies on structural characterization of in situ hypervalent iodine species and reaction mechanism

Further study on the structural properties of active hypervalent iodine species present in the catalytic system was conducted with the help of ESI/HR-MS and NMR techniques.

It was indicated that both hydroxy(aryl)iodonium salt (M^+ = 264.9369) and its dimeric form (M^+ = 510.8551) were simultaneously generated in the reaction mixture. In addition to spectroscopic and spectrometric analyses, single crystal X-ray crystallographic technique was also employed to confirm the structure of both hypervalent iodine species. As mentioned above, the monomeric hydroxy(aryl)iodonium was isolated in the form of triflate salt. Similarly, dimeric species which was able to be isolated from the solution by slow evaporation was also identified as the triflate salt co-crystallized with acetonitrile solvent.

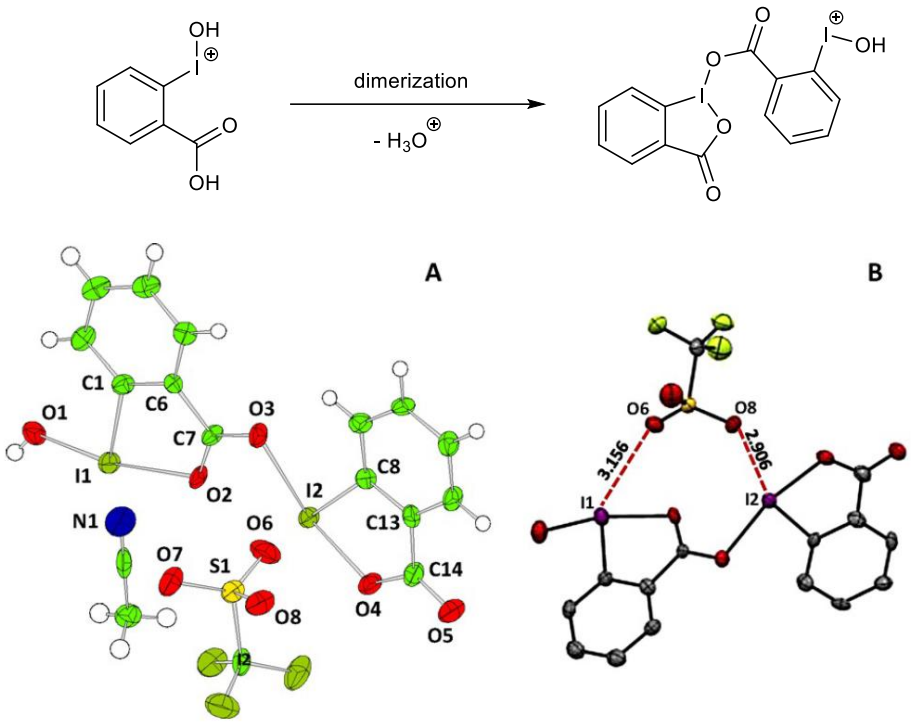
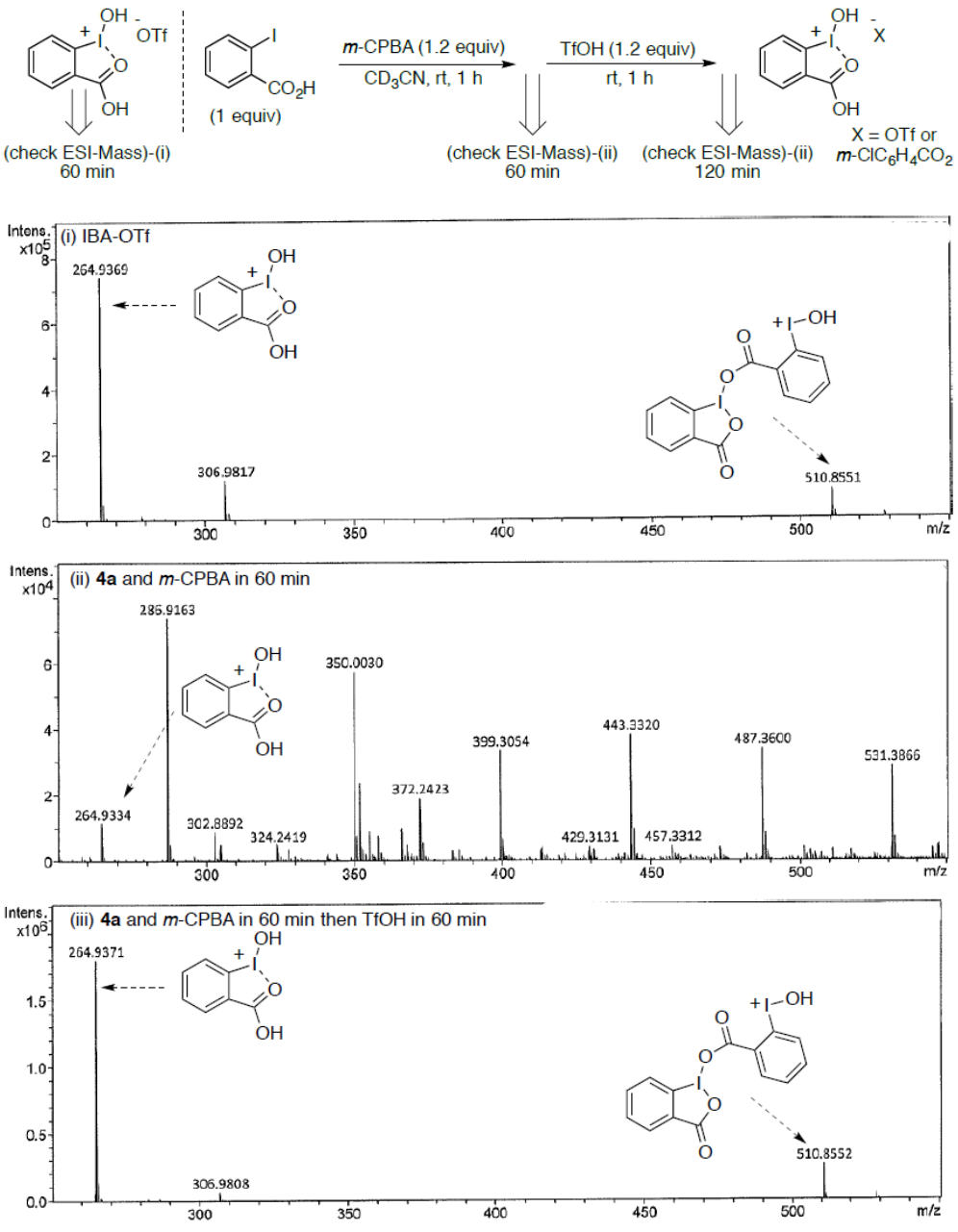


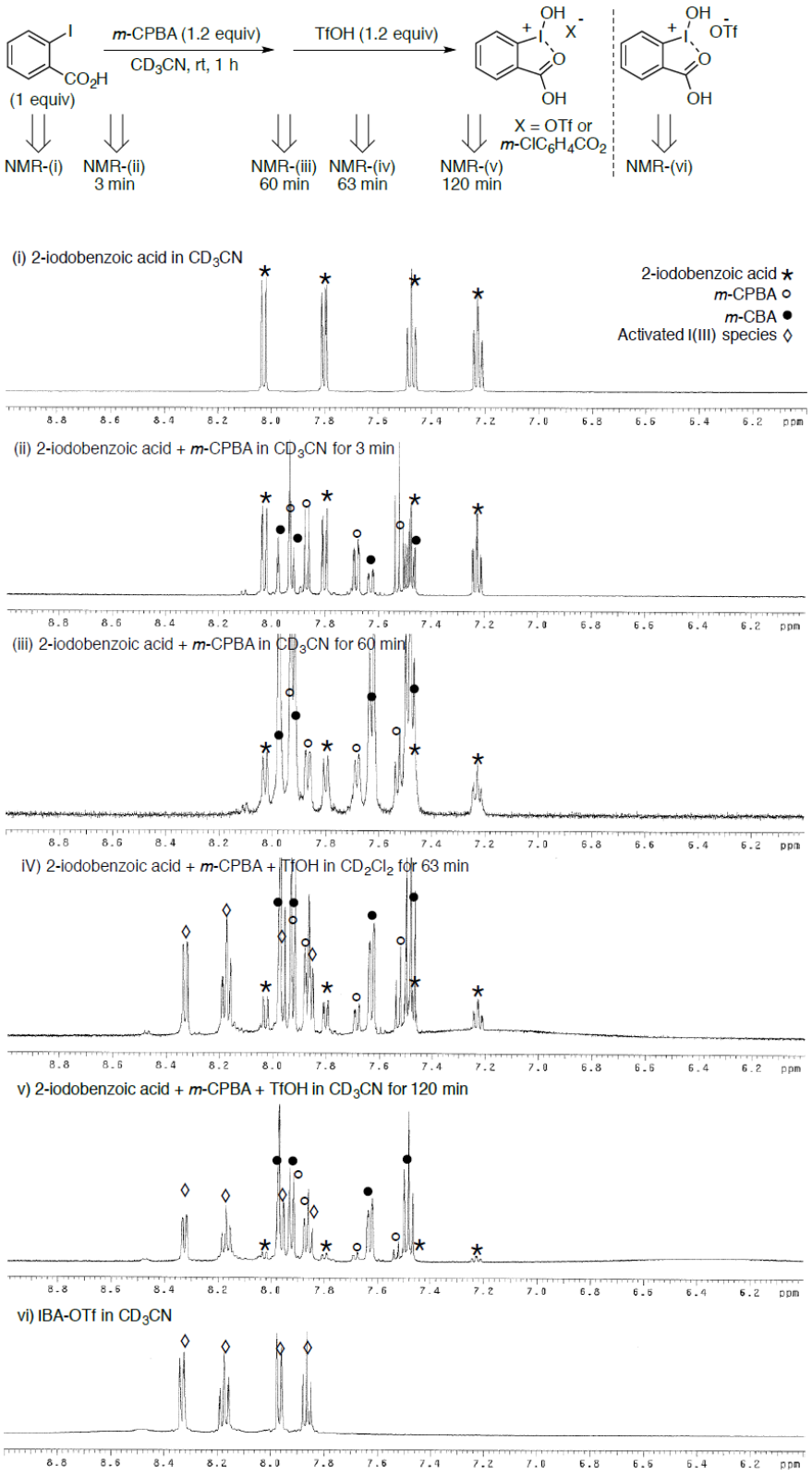
Figure 10. The formation of dimeric hypervalent iodine species from IBA-OTf, its X-ray crystal structure with triflate anion and the solvent acetonitrile molecule (A) and its intermolecular interaction motif in the crystal (B).

Technically, two forms of hypervalent iodine species can be obtained from the *m*-CPBA-mediated oxidation of 2-iodobenzoic acid **2a**. Without TfOH, only monomeric species was formed in a trace amount which can be only detected from ESI-MS (264.9335). The cycloaddition in the absence of TfOH, therefore, only afforded the cycloadduct **3a** in very poor NMR yield of 3% (entry 2, Table 2). However, the generation of active hydroxy(aryl)iodonium species was significantly accelerated by

adding a stoichiometric amount of TfOH to the in-process reaction mixture of **2a** and *m*-CPBA in CD_3CN. After one further hour of stirring at room temperature, the monomeric and dimeric active hydroxy(aryl)iodonium species were formed in quantitative amounts which can be easily seen from ESI-Mass as well as NMR spectroscopy (Scheme 45 and 46).

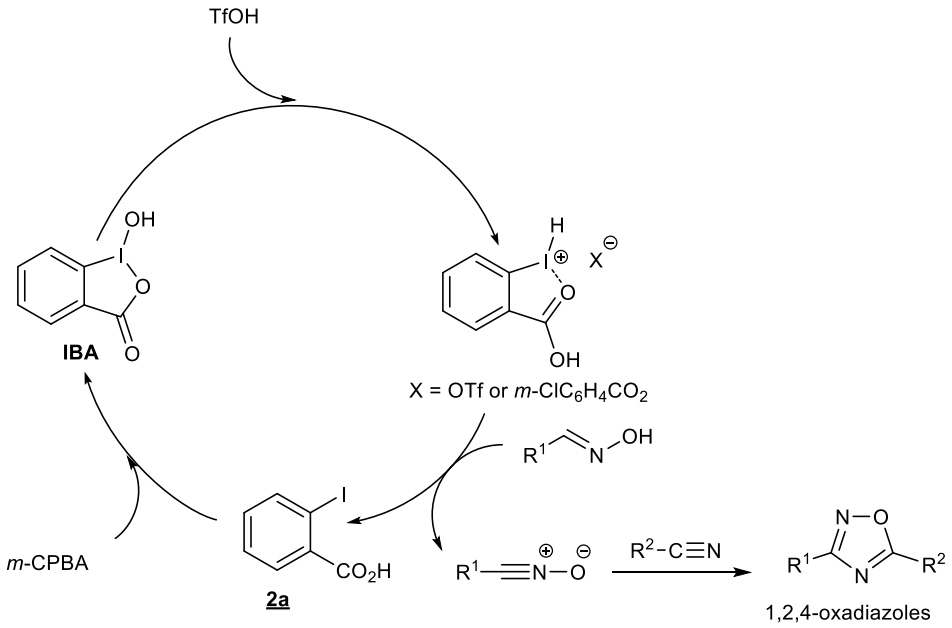


Scheme 45. Structural study of active hypervalent iodine species in solvent CH_3CN by ESI-MS spectrometry.



Scheme 46. Structural study of active hypervalent iodine species in solvent CD_3CN by NMR spectroscopy.

Based on the structural study of *in situ* IBA-OTf as well as previously reported research on similar cycloadditions of aldoximes using other hypervalent iodine reagents, we proposed herein the catalytic reaction mechanism as depicted in Scheme 47. The active monomeric hydroxy(aryl)iodonium salts (and possibly dimeric form), which are catalytically generated from 2-iodobenzoic acid **2a** and *m*-CBPA in the presence of TfOH, undergo the redox reaction with aldoximes to produce the corresponding nitrile oxides and recovered 2-iodobenzoic acid **2a**. The consecutive pericyclic cycloaddition between freshly generated nitrile oxides and nitriles as trapping agents to furnish the isolable 1,2,4-oxadiazoles. The *in situ* recovered 2-iodobenzoic acid **2a** can be reoxidized to active hypervalent iodine species for the next catalytic cycle.



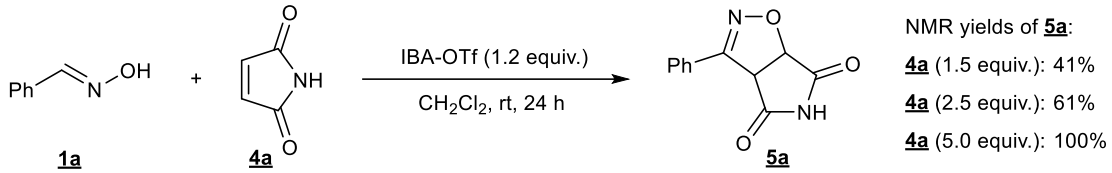
Scheme 47. Proposed mechanism for the catalytic formation of 1,2,4-oxadiazoles.

3.4. IBA-OTf mediated formation of pyrrolo-isoxazoles in catalytic condition

3.4.1. Optimization study

The oxidative performance of IBA-OTf was tested on the cycloaddition of benzaldoxime **1a** to maleimide **4a** to form pyrrolo-isoxazole adduct **5a** whose best NMR yield was up to 100% when 5 equiv of **4a** was added to the reaction mixture. The attempt to obtain **5a** in quantitative yield with a lower equivalent of **4a** was unsuccessful. Although no starting material **1a** was detected in the resulting mixture after the reaction,

only 41-61% recovery of the desired product was recorded (Scheme 46). Further analyses on the aqueous solution obtained after work-up steps revealed the presence of benzoic acid as the main by-product whose composition was 40% and 37% when 1.5 and 2.5 equivalent of **4a** were added to the reaction mixture, respectively.

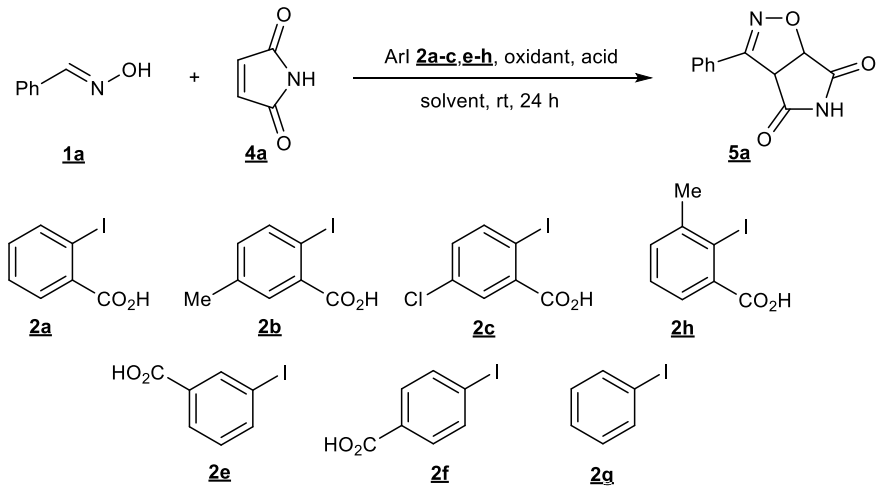


Scheme 48. Non-catalytic oxidative cycloaddition of benzaldoxime to maleimide using IBA-OTf as the oxidant.

The formation of pyrrolo-isoxazole **5a** deriving from benzaldoxime **1a** was then also used as the model reaction in the search for optimal conditions of catalytic oxidative cycloaddition (Table 4). The fact that no reaction was observed in the absence of iodoarene **2a** confirmed the necessity of hypervalent iodine species (entry 1). Even a small amount of 5-10 mol% of **2a** can induce a quantitative conversion of **1a** to **5a** whose NMR yield was over 80% (entry 2 and 3). Interestingly, the reaction can occur without TfOH (entry 4) to give **5a** in 72% NMR yield because of the presence of some *in situ* hypervalent iodine species generated from the oxidation of **2a** by *m*-CPBA, such as IBA and IBA-*m*-CBA. However, a gradual decrease in yield of **5a** was unavoidable when the equivalent of TfOH was reduced from 1.2 to none (entry 3-5). In a similar way to the non-catalytic procedure, using less than 5 equivalent of **4a** also resulted in moderate yields of **5a** (entry 7 and 8). The study on the pre-catalytic performance of various iodoarenes indicated that both **2a** and **2b** are the most active species which can afford **5a** in the isolated yields of 85 and 88%, respectively. Iodoarene **2a** was then chosen for the following study on substrate scope due to its less costly commercial availability. A subsequent solvent scope study was performed on a variety of polar and nonpolar solvents. It was apparently concluded that the reaction was favored in moderately polar solvents such as dichloromethane, chloroform, 1,1,2,2-tetrachloroethane, and ethyl acetate to give the adduct **5a** in excellent NMR yields of over 95% (entry 3, 15-17) while a typical non-polar solvent as hexane resulted in a significantly lessened yield of **5a** (entry 18). The reaction in methanol, however, only furnished a trace amount of desired

product **5a** because of the competitive esterification of methanol by benzoic acid to form methyl benzoate as the main product (entry 19).

Table 4. Optimization study for the hypervalent iodine-mediated cyclization of benzaldoxime with maleimide.



Entry	Solvent	**4a** (equiv.)	ArI (equiv.)	*m*-CPBA (equiv.)	TfOH (equiv.)	**5a** (%)[a]
1	CH_2Cl_2	5.0	none	1.5	1.2	none
2	CH_2Cl_2	5.0	**2a** (0.05)	1.5	1.2	86
3	CH_2Cl_2	5.0	**2a** (0.1)	1.5	1.2	100 (85)
4	CH_2Cl_2	5.0	**2a** (0.1)	1.5	0.6	93
5	CH_2Cl_2	5.0	**2a** (0.1)	1.5	none	72
6	CH_2Cl_2	5.0	**2a** (0.1)	1.2	0.6	80
7	CH_2Cl_2	2.5	**2a** (0.1)	1.5	1.2	59
8	CH_2Cl_2	1.5	**2a** (0.1)	1.5	1.2	54
9	CH_2Cl_2	5.0	**2b** (0.1)	1.5	1.2	100 (88)
10	CH_2Cl_2	5.0	**2c** (0.1)	1.5	1.2	78
11	CH_2Cl_2	5.0	**2h** (0.1)	1.5	1.2	85
12	CH_2Cl_2	5.0	**2e** (0.1)	1.5	1.2	95
13	CH_2Cl_2	5.0	**2f** (0.1)	1.5	1.2	95
14	CH_2Cl_2	5.0	**2g** (0.1)	1.5	1.2	75
15	$(CHCl_2)_2$	5.0	**2a** (0.1)	1.5	1.2	96 (82)
16	$CHCl_3$	5.0	**2a** (0.1)	1.5	1.2	95

17	EtOAc	5.0	**2a** (0.1)	1.5	1.2	95
18	*n*-Heptane	5.0	**2a** (0.1)	1.5	1.2	66
19	MeOH	5.0	**2a** (0.1)	1.5	1.2	Trace

[a] Yields are calculated from ^{1}H NMR spectra of reaction mixtures using 1,1,2,2-tetrachloroethane as internal standard (numbers in parentheses are reported as isolated yields).

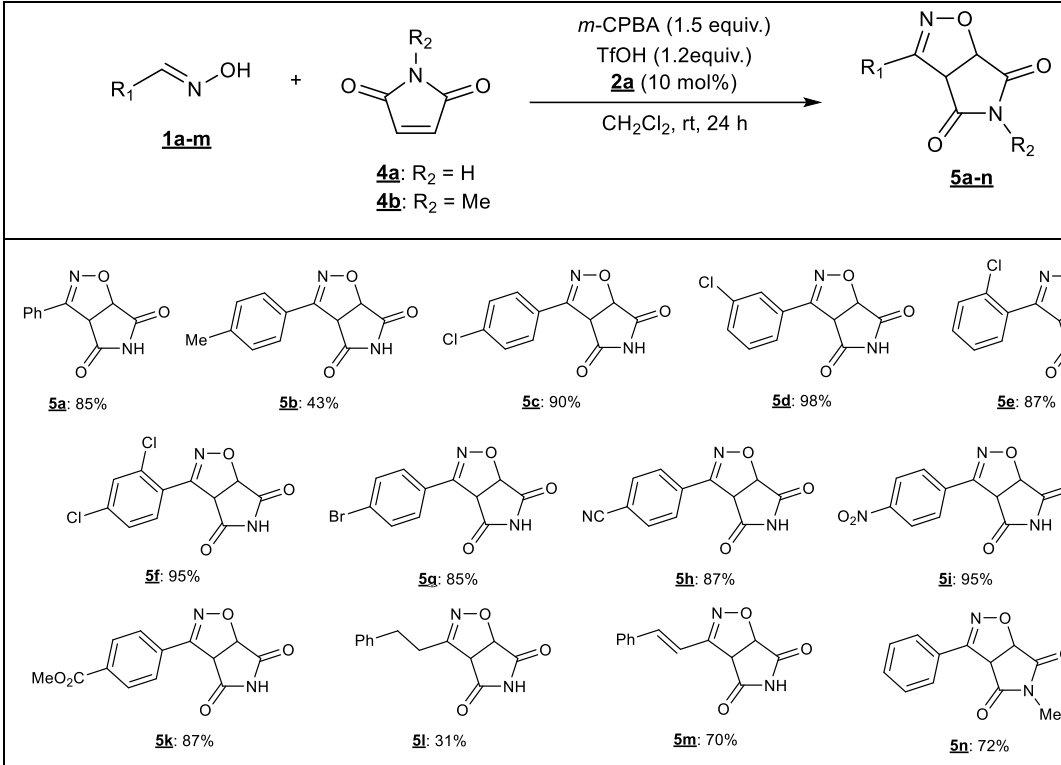
3.4.2. Substrate scope and reaction mechanism study

It can be seen from the Table 5 that the reaction of aromatic aldoximes bearing electron-withdrawing or electron-donating substituents in general afforded the corresponding pyrrolo-isoxazole adducts in good yields (85-98%). These results make sense when the stabilization of *in situ* generated nitrile oxides by electrostatic interactions is counted as a critical factor deciding the reaction yield. As mentioned previously in the introduction section, the presence of electron-withdrawing or electron-donating substituents, especially those in the *para* position of the benzene ring, is essential for the stabilization of nitrile oxide via inductive or resonance effect-induced delocalization of the positive as well as negative charge of the carbon in nitrile oxide moiety. The only exceptional low yield of **5b** (43%) can be explained based on the fact that the methyl group or electron-rich aromatic ring was oxidized in competition with cycloaddition to produce water-soluble by-products which were not recovered after the treatment with $NaHCO_3$ solution during the work-up step. Likewise, the assumption that carbon-carbon double is probably oxidized under the investigated reaction conditions can also be applicable to explain the slightly weak reactivity of **1m** towards cycloaddition when the desired adduct **5m** was only achieved in a fair isolated yield of 70%. Interestingly, in spite of the presence of *O*-substituted bulky chlorine group in **1e** and **1f**, the corresponding cycloadducts **5e** and **5f** were still isolated in good yields of 87% and 95%, respectively. This result is presumably due to the domination of electrostatic effect over steric effect.

As expected, the nitrile oxide generated from aliphatic aldoxime **1l** was unstable because of the lack of extended conjugation. As a result, the localized charge on the nitrile oxide functional group made this species overreactive and quickly destroyed

before reacting with maleimide to give the desired product **5l** in a poor yield (31%). Furthermore, the fact that the acidic methylene moiety adjacent to the benzene ring is likely suffered from competitive oxidation was also considered as the secondary factor contributing to the extremely low yield of **5l**.

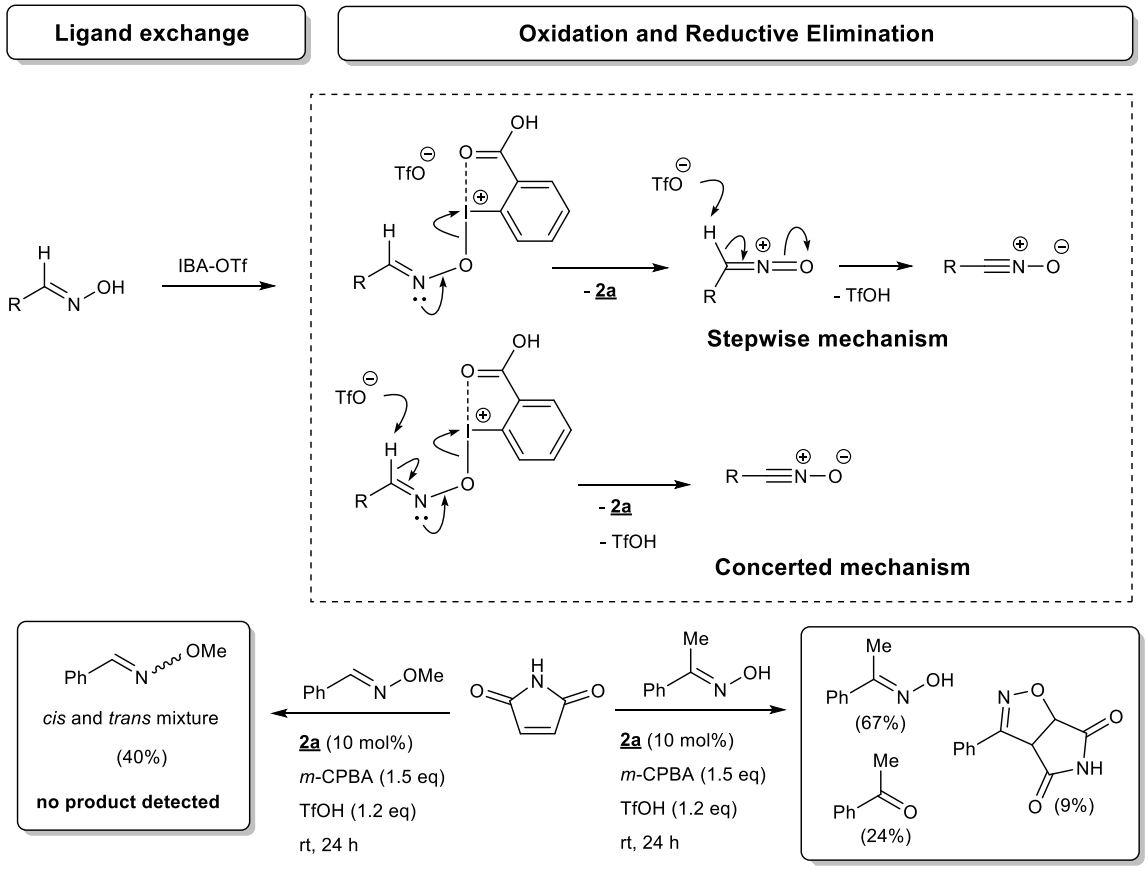
Table 5. Study on reactant scope of oxidative cyclization of aldoximes with maleimide using catalytic IBA-OTf.[a, b]



[a] Reagents and conditions: aldoximes (0.250 mmol), maleimide **4a** or **4b** (1.250 mmol), *m*-CPBA (0.375), TfOH (0.300 mmol), and 2-iodobenzoic acid (0.025 mmol) in dichloromethane (2 mL) at room temperature for 24 h. [b] Isolated yields.

Additionally, some control experiments were also performed to study the mechanism of the [3+2] catalytic cycloaddition of benzaldoximes with maleimide in particular and other dipolarophiles in general. In the proposed mechanism, the generation of nitrile oxides from benzaldoximes was depicted as a two-step process consisting the ligand exchange and oxidation step. The existence of the ligand exchange step can be verified by the reaction of maleimide **4a** with the protected benzaldoxime, *O*-

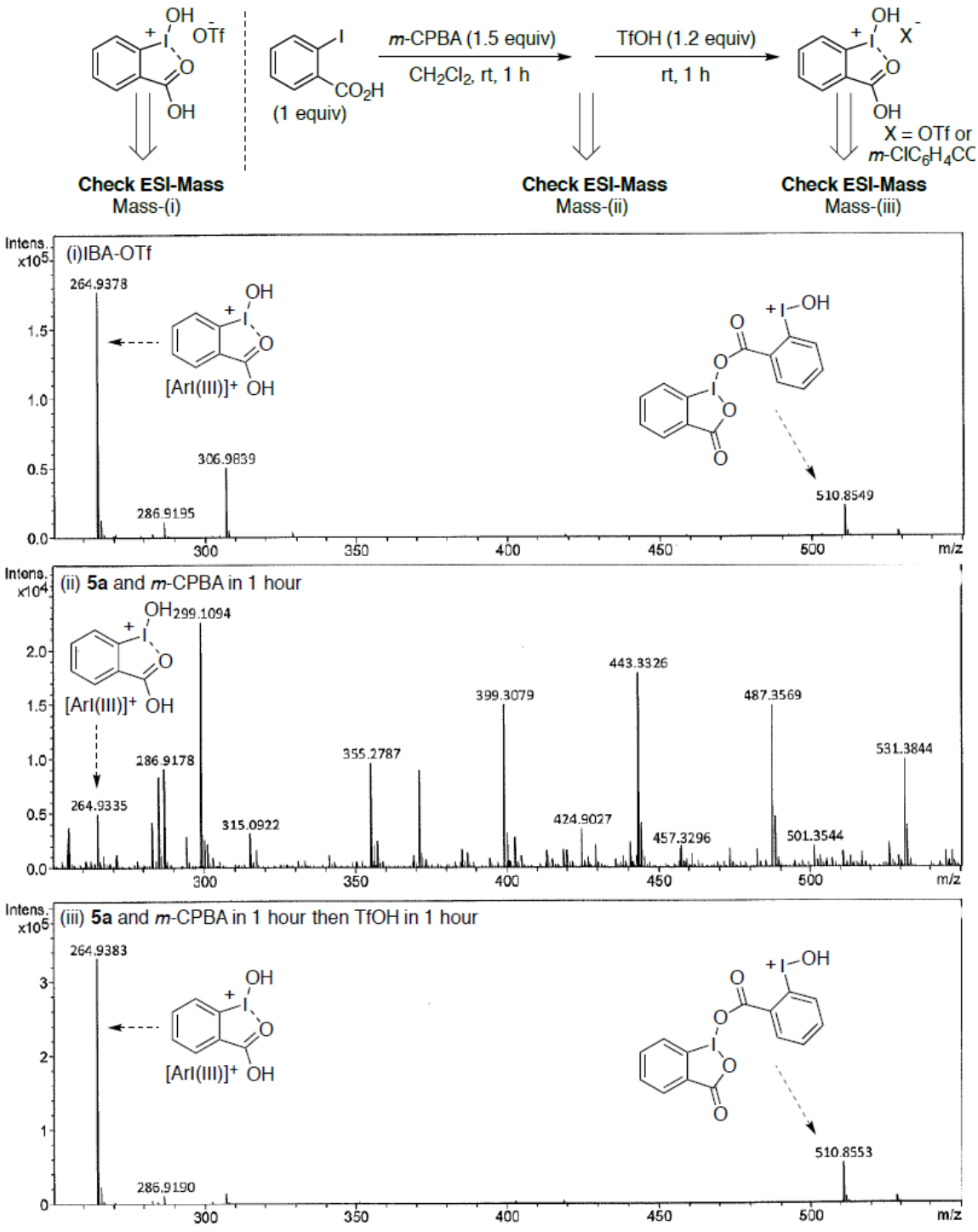
methylbenzaldoxime. The fact that no cycloadduct **5a** was detected under the optimized conditions straightforwardly demonstrated the requirement of the ligand exchange step to initiate the formation of nitrile oxides. In a similar way, the second control reaction between maleimide **4a** and acetophenone oxime was performed to test the necessity of the oxidation step. Only trace amount of the cycloadduct **5a** was detected while unreacted starting material, along with the by-product acetophenone, was recovered from the reaction mixture in quantitative yields. This results indicated that oxidation step also played a major role in the formation of nitrile oxides.



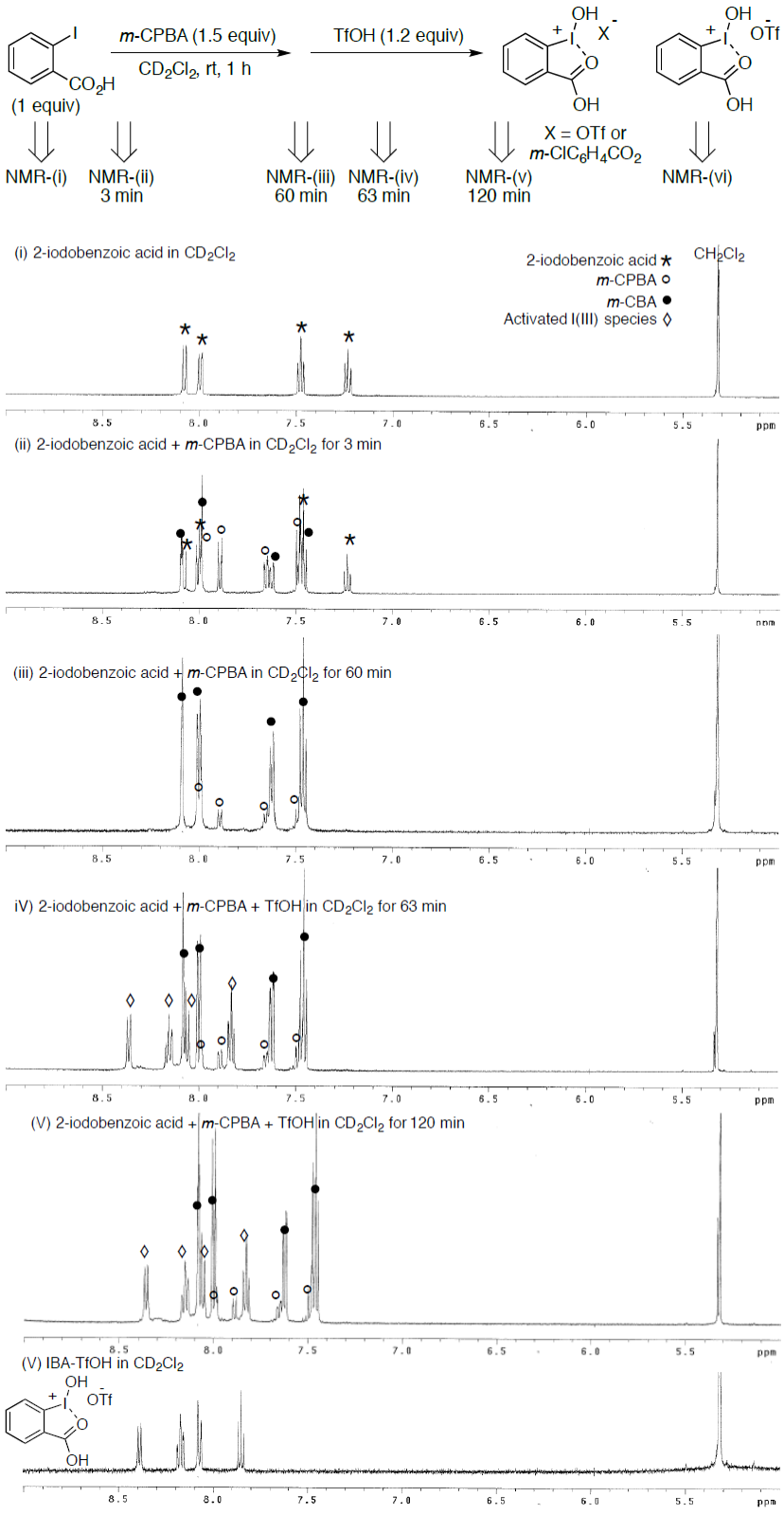
Scheme 49. Proposed mechanism for IBA-OTf assisted generation of nitrile oxide through a two-step process of ligand exchange and oxidation-reductive elimination and blank experiments for confirmation.

Further study on mechanism showed that this reaction was induced by the active hydroxy(aryl)iodonium species generated from the *m*-CPBA-mediated oxidation of 2-iodobenzoic acid **2a**. Without TfOH, this active species was formed in a trace amount

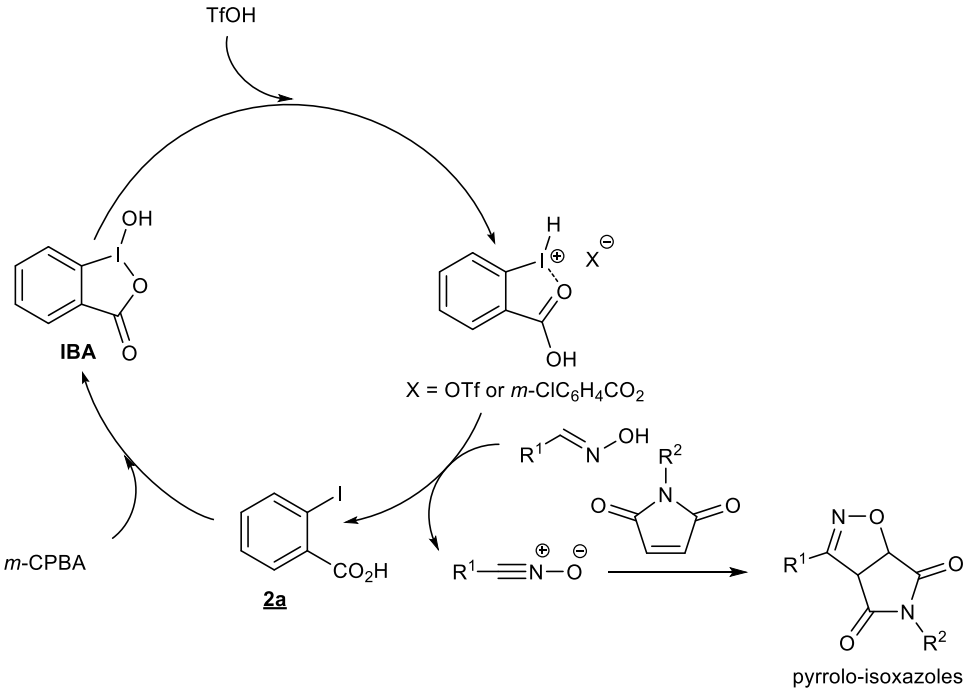
which can be only detected by ESI-Mass spectroscopy (264.9335). The cycloaddition, therefore, was still able to proceed in the absence of TfOH to afford the pyrrolo-isoxazole **5a** in a fair NMR yield of 72% (entry 5, Table 4). However, the generation of active hydroxy(aryl)iodonium species was significantly accelerated by adding a stoichiometric amount of TfOH to the in-process reaction mixture of **2a** and m-CPBA in CH_2Cl_2. After one further hour of stirring at room temperature, the active hydroxy(aryl)iodonium species was formed in a quantitative amount which can be easily seen from ESI-MS as well as NMR spectroscopy. As expected, the catalytic cycloaddition in the presence of TfOH as an additive can approach the completion to give the pyrrolo-isoxazole **5a** in excellent NMR yield of 100% (entry 3, Table 4).



Scheme 50. Structural study of active hypervalent iodine species in solvent CH_2Cl_2 by ESI-MS spectrometry.



Scheme 51. Structural study of active hypervalent iodine species in solvent CD_2Cl_2 by NMR spectroscopy.



Scheme 52. A plausible mechanism for the catalytic formation of pyrrolo-isoxazoles.

4. EXPERIMENTAL SECTION

4.1. Chemicals and equipment

- All chemicals and solvents were purchased from Sigma–Aldrich and employed without further purification. Silica gel for column chromatography and preparative thin layer chromatography plates were from Dynamic Adsorbents Inc. and Analtech, respectively. All the reactions were carried out under dry argon atmosphere using moisture free glassware. Acetonitrile and dichloromethane which were used as reaction media must be freshly distilled from CaH_2 before use.
- Ohaus Adventurer electronic semianalytical balance, model EPB-203.
- Electrothermal melting point apparatus, model MEL-TEMP 1101D.
- Eyela rotary evaporator system, model N-1001.
- Barnstead Thermolyne CIMAREC magnetic stirrer, model S131125
- Agilent GC system, model 7890A, equipped with a Mass selective detector Agilent 5975C VL MSD and a capillary column DB-5MS (60 m x 0.25 mm x 0.3 μm).
- Perkin-Elmer 1600 series FT-IR.
- Bruker micrOTOF-Q II HR-MS instrument.
- Single crystal X-ray diffractometer Rigaku RAPID II Image Plate, equipped with a graphite-monochromated MoKα radiation source (λ = 0.71073 Å).
- Varian Inova 500 NMR spectrometer was used to record all ^{1}H NMR spectra of the products at 500 MHz.
- Varian Mercury 300 NMR spectrometer was used to record all ^{13}C NMR spectra of the products at 75 MHz.
- Welch DuoSeal vacuum pump, model 1399B-01, equipped with a Schlenk line.

4.2. Typical procedure for the preparation of aldoximes

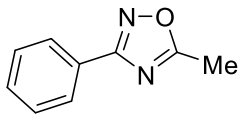
A flask (50 mL volume) was charged with a corresponding precursor aldehyde (5 mmol), hydroxyamine hydrochloride (695 mg, 10 mmol), pyridine (1528 mg, 20 mmol), and dichloromethane (25 mL). The reaction mixture was stirred at room temperature for 20 h. Upon completion, the resulting solution was washed with HCl 10% (15 mL) and subsequently with water. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. Further purification

was performed on column chromatography with silica gel and eluent solvent of hexane/ethyl acetate to afford the corresponding oxime as white to yellow solid.

4.3. Typical procedure and spectral data for the preparation of 1,2,4-oxadiazoles

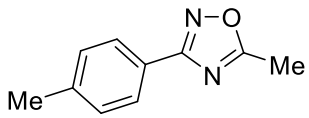
Method A: 2-Iodobenzoic acid **2a** (3.1 mg, 0.0125 mmol), *m*-CPBA (52 mg, 0.300 mmol), and trifluoromethylsulfonic acid (45 mg, 0.300 mmol) were added to a solution of aldoxime **1a**-**c**, **1h**-**m** (0.250 mmol) in 2.0 mL of the appropriate nitrile solvent. The reaction mixture was stirred at room temperature for 24 h. Upon completion, the reaction was quenched by adding 5% aqueous $Na_2S_2O_3$ (2 mL) and then saturated $NaHCO_3$ (5 mL). The resulting mixture was then extracted with dichloromethane. The organic portion was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude products. Further purification was performed on column chromatography with silica gel and eluent solvent of hexane/ethyl acetate to afford the corresponding 1,2,4-oxadiazoles as white to yellow solids.

5-Methyl-3-phenyl-1,2,4-oxadiazole (**3a**)



Reaction of benzaldehyde oxime **1a** (30 mg, 0.25 mmol) and acetonitrile according to the general procedure afforded product **3a** (33 mg, 83%) as a white solid: mp 38.9 - 39.1 ^{o}C; ^{1}H NMR (500 MHz, TMS, $CDCl_3$): δ (ppm) 8.07-8.05 (m, 2H), 7.50-7.43 (m, 3H), 2.66 (s, 3H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ (ppm) 176.8, 168.6, 131.3, 129.1, 127.6, 127.1, 12.6.

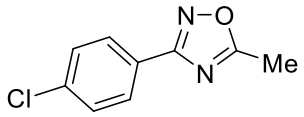
5-Methyl-3-(p-tolyl)-1,2,4-oxadiazole (**3b**)



Reaction of 4-methylbenzaldehyde oxime **1b** (34 mg, 0.25 mmol) and acetonitrile according to the general procedure afforded product **3b** (37 mg, 84%) as a white solid: mp 78.5 - 79.7 °C; ^{1}H NMR (500 MHz, TMS, $CDCl_3$): δ (ppm) 7.95 (d, J = 7.8 Hz, 2H),

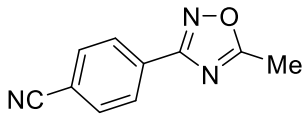
7.27 (d, J = 7.8 Hz, 2H), 2.65 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ (ppm) 176.3, 168.4, 141.4, 129.5, 127.3, 124.0, 21.5, 12.4.

3-(4-Chlorophenyl)-5-methyl-1,2,4-oxadiazole (**3c**)



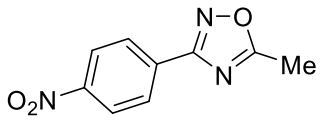
Reaction of 4-chlorobenzaldehyde oxime **1c** (38 mg, 0.25 mmol) and acetonitrile according to the general procedure afforded product **3c** (38 mg, 78%) as a white solid: mp 92.8 - 93.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.00 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.3 Hz, 2H), 2.66 (s, 3H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ (ppm) 176.7, 167.6, 137.3, 129.2, 128.7, 125.3, 12.4.

4-(5-Methyl-1,2,4-oxadiazol-3-yl)benzonitrile (**3h**)



Reaction of 4-cyanobenzaldehyde oxime **1h** (36 mg, 0.25 mmol) and acetonitrile according to the general procedure afforded product **3h** (34 mg, 74%) as a white solid: mp 114.9 - 117.0 °C; IR (CH_2Cl_2) cm^{-1} 3077, 3059, 2923, 2853, 2230, 1592, 1557, 1047; ^{1}H NMR (500 MHz, TMS, $CDCl_3$): δ (ppm) 8.19 (d, J = 8.3 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H), 2.69 (s, 3H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ (ppm) 177.3, 167.1, 132.6, 131.0, 127.9, 118.2, 114.7, 12.4. HR-MS (ESI-APSI-negative ionization): calcd for $C_{10}H_7N_3O$ ($[M]^+$): 185.0589, found: 185.0588.

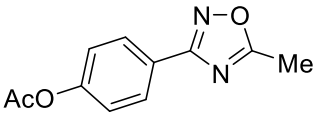
5-Methyl-3-(4-nitrophenyl)-1,2,4-oxadiazole (**3i**)



Reaction of 4-nitrobenzaldehyde oxime **1i** (42 mg, 0.25 mmol) and acetonitrile according to the general procedure afforded product **3i** (34 mg, 67%) as a white solid: mp 145.0 - 146.8 °C; IR (CH_2Cl_2) cm^{-1} 3099, 2923, 2853, 1520, 1349, 1049; ^{1}H NMR (500

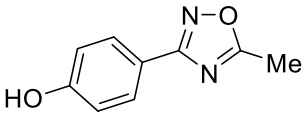
MHz, TMS, $CDCl_3$): δ (ppm) 8.34 (d, J = 7.0 Hz, 2H), 8.26 (d, J = 7.0 Hz, 2H), 2.70 (s, 3H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$) δ (ppm) 177.4, 166.9, 149.4, 132.7, 128.3, 124.1, 12.4.

4-(5-Methyl-1,2,4-oxadiazol-3-yl)phenyl acetate (**3j**)



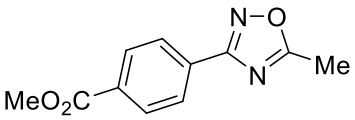
Reaction of 4-(hydroxyimino)methyl-phenyl acetate **1j** (44 mg, 0.25 mmol) and acetonitrile according to the general procedure afforded product **3j** (17 mg, 31%) and deacylated product **3j'** (25 mg, 56%). The product **3j** was isolated as a white solid: mp 115.5 - 117.4 °C; IR (CH_2Cl_2) cm^{-1} 3007, 2927, 2862, 1756, 1540, 1217, 1047; ^1H NMR (500 MHz, TMS, $CDCl_3$): δ (ppm) 8.09 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.5 Hz, 2H), 2.65 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ (ppm) 176.6, 169.1, 167.7, 152.8, 128.7, 124.5, 122.1, 21.2, 12.4.

4-(5-Methyl-1,2,4-oxadiazol-3-yl)phenol (**3j'**)



The product **3j'** was isolated as a white solid: mp 188.4 - 190.0 °C; IR (CH_2Cl_2) cm^{-1} 3424, 2923, 2857, 1540, 1047; ^1H NMR (500 MHz, TMS, $CDCl_3$): δ (ppm) 7.85 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 2.61 (s, 3H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ (ppm) 176.9, 168.0, 160.3, 128.6, 117.6, 115.3, 10.6.

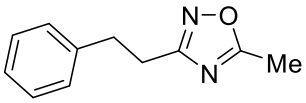
Methyl 4-(5-methyl-1,2,4-oxadiazol-3-yl)benzoate (**3k**)



Reaction of methyl-4-(hydroxyimino)methylbenzoate **1k** (44 mg, 0.25 mmol) and acetonitrile according to the general procedure afforded product **3k** (40 mg, 73%) as a white solid: mp 164.8 - 165.5 °C; IR (CH_2Cl_2) cm^{-1} 3015, 2923, 2857, 1717, 1700, 1538,

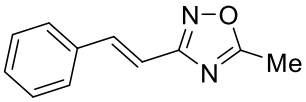
1279, 1049; ^{1}H NMR (500 MHz, TMS, $CDCl_3$): δ (ppm) 8.14 (s, 4H), 3.95 (s, 3H), 2.68 (s, 3H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ (ppm) 177.2, 168.0, 166.6, 132.6, 131.1, 130.3, 127.6, 52.6, 12.6.

5-Methyl-3-phenethyl-1,2,4-oxadiazole (**3l**)



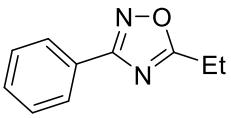
Reaction of 3-phenylpropanal oxime **1l** (38 mg, 0.25 mmol) and acetonitrile according to the general procedure afforded product **3l** (33 mg, 70%) as a colorless oil; IR (CH_2Cl_2) cm^{-1} 3059, 3029, 2928, 2857, 1588, 1456, 1049; ^{1}H NMR (500 MHz, TMS, $CDCl_3$): δ (ppm) 7.30 (t, J = 7.3 Hz, 2H), 7.25 - 7.21 (m, 3H), 3.06 – 3.00 (m, 4H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ (ppm) 176.3, 169.9, 140.3, 128.5, 128.3, 126.4, 33.0, 27.8, 12.3; HR-MS (ESI-positive ionization): calcd for $C_{11}H_{12}N_2O$ ($[M+H]^+$): 189.1028, found: 189.0998.

(E)-5-Methyl-3-styryl-1,2,4-oxadiazole (**3m**)



Reaction of cinnamaldehyde oxime **1m** (36 mg, 0.25 mmol) and acetonitrile according to the general procedure afforded product **3m** (29 mg, 62%) as a white solid: mp 79.0 - 80.5 °C; ^{1}H NMR (500 MHz, TMS, $CDCl_3$): δ (ppm) 7.67 (d, J = 16.0 Hz, 1H), 7.56 (d, J = 7.0 Hz, 2H), 7.43 - 7.33 (m, 3H), 7.05 (d, J = 16.0 Hz, 1H), 2.62 (s, 3H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ (ppm) 175.8, 167.9, 138.9, 135.3, 129.4, 128.9, 127.4, 112.8, 12.3.

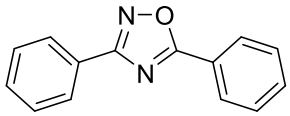
5-Ethyl-3-phenyl-1,2,4-oxadiazole (**3o**)



Reaction of benzoaldoxime **1a** (30 mg, 0.25 mmol) and propionitrile according to the general procedure afforded product **3o** (30 mg, 70%) as a colorless oil; ^{1}H NMR (500

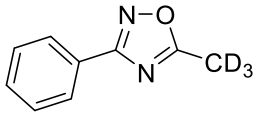
MHz, TMS, $CDCl_3$): δ (ppm) 8.09 - 8.06 (m, 2H), 7.50 - 7.47 (m, 3H), 2.98 (q, J = 7.5 Hz, 2H), 1.46 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ (ppm) 180.7, 168.3, 131.0, 128.8, 127.4, 127.0, 20.3, 10.8.

3,5-Diphenyl-1,2,4-oxadiazole (**3r**)



Reaction of benzaldoxime **1a** (30 mg, 0.25 mmol) and benzonitrile according to the general procedure afforded product **3r** (35 mg, 63%) as a white solid: mp 108.0-109.5 °C; ^{1}H NMR (500 MHz, TMS, $CDCl_3$): δ (ppm) 8.23 (d, J = 8.0 Hz, 2H), 8.21 - 8.17 (m, 2H), 7.61 - 7.51 (m, 6H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ (ppm) 175.9, 169.2, 133.0, 131.4, 129.3, 129.1, 128.4, 127.8, 127.2, 124.6.

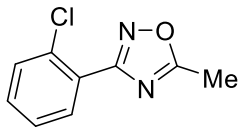
5-(Methyl-d_3)-3-phenyl-1,2,4-oxadiazole (**3s**)



Reaction of benzaldoxime **1a** (30 mg, 0.25 mmol) and acetonitrile-d_3 according to the general procedure afforded product **3s** (18 mg, 44%) as a yellow liquid; ^{1}H NMR (500 MHz, TMS, $CDCl_3$): δ (ppm) 8.08 - 8.06 (m, 2H), 7.52 - 7.46 (m, 3H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ (ppm) 176.4, 168.4, 131.1, 128.8, 127.3, 126.8, 11.7.

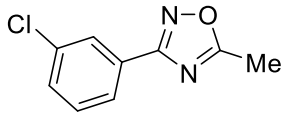
Method B: 2-Iodobenzoic acid **2a** (6.2 mg, 0.025 mmol), *m*-CPBA (65 mg, 0.375 mmol), and trifluoromethylsulfonic acid (45 mg, 0.300 mmol) were added to a solution of aldoxime **1d**-**g** (0.250 mmol) in 2.0 mL of the appropriate nitrile solvent. The reaction mixture was then stirred at room temperature for 24 h. Upon completion, the work-up and purification procedure was conducted in a similar way as described in Method A to afford the corresponding 1,2,4-oxadiazoles as white to yellow solids.

3-(2-Chlorophenyl)-5-methyl-1,2,4-oxadiazole (**3d**)



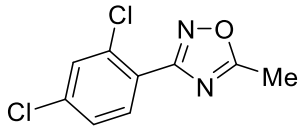
Reaction of 2-chlorobenzaldehyde oxime **1d** (38 mg, 0.25 mmol) and acetonitrile according to the general procedure afforded product **3d** (40 mg, 82%) as a yellow oil; IR (neat) cm^{-1} 2927, 2857, 1558, 1049; ^{1}H NMR (500 MHz, TMS, $CDCl_3$): δ (ppm) 7.89 (dd, J = 7.8 and 1.8 Hz, 1H), 7.54 (dd, J = 7.8 and 1.3 Hz, 1H), 7.42 (dd, J = 7.8 and 1.8 Hz, 1H), 2.69 (s, 3H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ (ppm) 176.1, 167.3, 133.4, 131.6, 131.6, 130.9, 126.9, 126.2, 12.4.

3-(3-Chlorophenyl)-5-methyl-1,2,4-oxadiazole (**3e**)



Reaction of 2-chlorobenzaldehyde oxime **1e** (38 mg, 0.25 mmol) and acetonitrile according to the general procedure afforded product **3e** (42 mg, 86%) as colorless needles: mp 69.5 - 71.3 °C; IR (CH_2Cl_2) cm^{-1} 3064, 2927, 2862, 1558, 1075; ^{1}H NMR (500 MHz, TMS, $CDCl_3$): δ (ppm) 8.06 (d, J = 1.5 Hz, 1H), 7.95 (dd, J = 8.0 and 1.5 Hz, 1H), 7.47 - 7.45 (m, 1H), 7.41 (t, J = 8.0 Hz, 1H), 2.65 (s, 3H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ (ppm) 176.8, 167.4, 134.9, 131.1, 130.1, 128.5, 127.4, 125.4, 12.3.

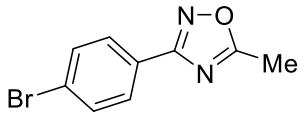
3-(2,4-Dichlorophenyl)-5-methyl-1,2,4-oxadiazole (**3f**)



Reaction of 2,4-dichlorobenzaldehyde oxime **1f** (48 mg, 0.25 mmol) and acetonitrile according to the general procedure afforded product **3f** (49 mg, 86%) as a white solid: mp 99.2 - 99.8 °C; IR (CH_2Cl_2) cm^{-1} 3066, 2927, 2853, 1587, 1060; ^{1}H NMR (500 MHz, TMS, $CDCl_3$): δ (ppm) 7.87 (d, J = 8.1 Hz, 1H), 7.56 (d, J = 2.1 Hz, 1H), 7.37 (dd, J =

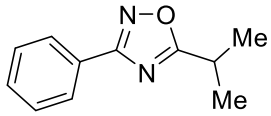
8.1 and 1.5 Hz, 1H), 2.68 (s, 3H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ (ppm) 176.5, 166.8, 137.4, 134.5, 132.6, 131.1, 127.6, 124.9, 12.6.

3-(4-Bromophenyl)-5-methyl-1,2,4-oxadiazole (**3g**)



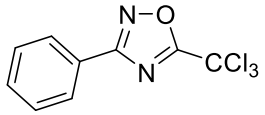
Reaction of 2,4-dichlorobenzaldehyde oxime **1g** (50 mg, 0.25 mmol) and acetonitrile according to the general procedure afforded product **3g** (45 mg, 75%) as a white solid: mp 99.1 - 99.9 °C; IR (CH_2Cl_2) cm^{-1} 3015, 2919, 2857, 1540, 1049; ^{1}H NMR (500 MHz, TMS, $CDCl_3$): δ (ppm) 7.93 (d, J = 7.5 Hz, 2H), 7.62 (d, J = 7.5 Hz, 2H), 2.65 (s, 3H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ (ppm) 176.8, 167.7, 132.1, 128.8, 125.8, 125.7, 12.4.

5-Isopropyl-3-phenyl-1,2,4-oxadiazole (**3p**)



Reaction of benzoaldoxime **1a** (30 mg, 0.25 mmol) and isobutylnitrile according to the general procedure afforded product **3p** (32 mg, 69%) as a colorless oil; IR (CH_2Cl_2) cm^{-1} 2923, 2857, 1540, 1049; ^{1}H NMR (500 MHz, TMS, $CDCl_3$): δ (ppm) 8.09 - 8.07 (m, 2H), 7.49 - 7.47 (m, 3H), 3.29 (sept, J = 7.0 Hz, 1H), 1.46 (d, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ (ppm) 183.9, 168.2, 131.0, 128.8, 127.4, 127.1, 27.6, 20.2.

3-Phenyl-5-(trichloromethyl)-1,2,4-oxadiazole (**3q**)

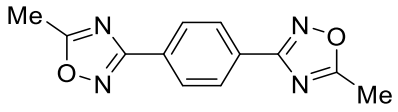


Reaction of benzoaldoxime **1a** (30 mg, 0.25 mmol) and 2,2,2-trichloroacetonitrile according to the general procedure afforded product **3q** (12 mg, 18%) as a colorless oil; ^{1}H NMR (500 MHz, TMS, $CDCl_3$): δ (ppm) 8.13 (d, J = 7.3 Hz, 2H), 7.58 - 7.51 (m,

3H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ (ppm) 174.4, 169.1, 132.0, 129.0, 127.7, 125.4, 83.5.

Method C:

1,4-bis(5-methyl-1,2,4-oxadiazol-3-yl)benzene (**3n**)

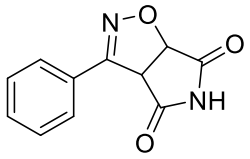


2-Iodobenzoic acid **2a** (6.2 mg, 0.025 mmol), *m*-CPBA (129 mg, 0.750 mmol), and trifluoromethylsulfonic acid (45 mg, 0.750 mmol) were added to a solution of terephthalaldehyde dioxime (113 mg, 0.250 mmol) in 2.0 mL of acetonitrile. The reaction mixture was stirred at room temperature for 24 h. Upon completion, the work-up and purification procedure was conducted in a similar way as described in Method A to afford 1,4-bis(5-methyl-1,2,4-oxadiazol-3-yl)benzene **3n** (53 mg, 88%) as a white solid: mp 220.5 - 225.0 °C; IR (CH_2Cl_2) cm^{-1} 2923, 2857, 1538, 1047; 1H NMR (500 MHz, TMS, $CDCl_3$): δ (ppm) 8.19 (s, 4H), 2.68 (s, 6H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ (ppm) 176.8, 167.8, 129.3, 127.8, 12.4. HR-MS (ESI-APCI-positive ionization): calcd for $C_{12}H_{10}N_4O_2$ ($[M+H]^+$): 243.0882, found: 243.0883.

4.4. Typical procedure and spectral data for the preparation of pyrrolo-isoxazoles

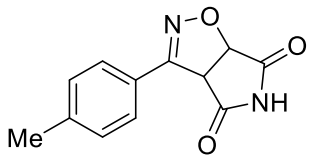
2-Iodobenzoic acid **2a** (6.2 mg, 0.025 mmol), maleimide **4a** or **4b** (1.25 mmol), *m*-CPBA (65 mg, 0.375 mmol), and trifluoromethylsulfonic acid (45 mg, 0.300 mmol) were added to a solution of aldoxime **1a**-**m** (0.250 mmol) in dichloromethane (2 mL). The reaction mixture was stirred at room temperature for 24 h. Upon completion, the reaction was quenched by adding 5% aqueous $Na_2S_2O_3$ (2 mL) and then saturated $NaHCO_3$ (5 mL). The resulting mixture was then extracted with ethyl acetate. The organic portion was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude products. Further purification was performed on column chromatography with silica gel and eluent solvent of hexane-ethyl acetate (3:1 and then 1:1) to afford the corresponding pyrrolo-isoxazoles **5a**-**n** as white to yellow solids.

3-Phenyl-3a,6a-dihydro-4*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*)-dione (**5a**)



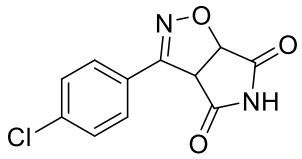
Reaction of benzaldoxime **1a** (30 mg, 0.250 mmol) and maleimide **4a** (121 mg, 1.25 mmol) according to the general procedure afforded product **5a** (46 mg, 85%) as a white solid; colorless prisms (recrystallized from methanol); mp 213-215 °C; IR (neat) cm^{-1} 1733, 1369, 1214; ^{1}H NMR (500 MHz, CD_3OD/ DMSO-*d*6= 20:1): δ (ppm) 7.99-7.97 (m, 2H), 7.50-7.46 (m, 3H), 5.52 (d, J = 9.5 Hz, 1H), 5.06 (d, J = 9.5 Hz, 1H); ^{13}CNMR (75 MHz, CD_3OD/ DMSO-*d*6= 20:1): δ (ppm) 174.5, 173.1, 153.9, 130.8, 128.7, 128.0, 127.7, 82.6, 56.4.

3-(*p*-Tolyl)-3a,6a-dihydro-4*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*)-dione (**5b**)

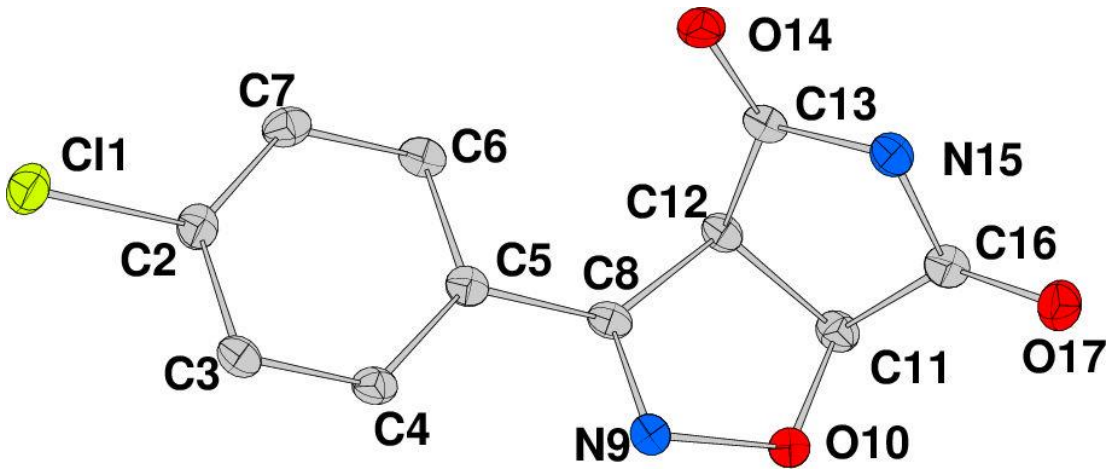


Reaction of *p*-methylbenzaldehyde oxime **1b** (34 mg, 0.250 mmol) and maleimide **4a** (121 mg, 1.25 mmol) according to the general procedure afforded product **5b** (25 mg, 43%) as an orange solid; orange plates (recrystallized from methanol); mp 182-185 °C; IR (neat) cm^{-1} 1734, 1336, 1193; ^{1}H NMR (500 MHz, CD_3OD): δ (ppm) 7.84 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H), 5.46 (d, J = 9.0 Hz, 1H), 4.98 (d, J = 9.0 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD): δ (ppm) 174.6, 173.0, 153.6, 141.3, 129.1, 127.9, 124.7, 82.3, 56.4, 20.3.

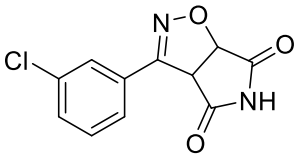
3-(4-Chlorophenyl)-3a,6a-dihydro-4*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*)-dione (**5c**)



Reaction of *p*-chlorobenzaldehyde oxime **1c** (39 mg, 0.250 mmol) and maleimide **4a** (121 mg, 1.25 mmol) according to the general procedure afforded product **5c** (56 mg, 90%) as a white solid; light yellow prisms (recrystallized from methanol); mp 196-198 °C; ^{1}H NMR (500 MHz, CD_3OD): δ (ppm) 7.94 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H), 5.50 (d, J = 9.5 Hz, 1H), 5.00 (d, J = 9.5 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ (ppm) 174.4, 172.9, 152.9, 136.6, 129.4, 128.7, 126.3, 82.8, 56.2. Single crystals of product **5c** suitable for X-ray crystallographic analysis were obtained by slow crystallization from the methanol. X-ray diffraction data for **4c** were collected on Rigaku RAPID II Image Plate system using graphite-monochromated MoKα radiation (λ = 0.71073 Å) at 123 K. The structure was solved by the Patterson method (SHELXS 86) and refined by full-matrix least-squares refinement on F^2 using Crystals for Windows program. Crystal data for **5c** $C_{11}H_7ClN_2O_3$: M 250.64, monoclinic, space group P21/n, a = 12.4723(4), b = 5.8635(2), c = 14.9153(10) Å, α = 90.00, β = 107.473(8), γ = 90.00 °, V = 1040.45(7) Å3, Z = 4, μ = 0.364 mm-1, 5358 reflections measured, 2246 unique (1924 I > 2.0/s(I)); final R_1 = 0.0386, R_w = 0.0986. CCDC-1470155.



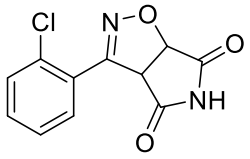
3-(3-Chlorophenyl)-3a,6a-dihydro-4*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*)-dione (**5d**)



Reaction of *m*-chlorobenzaldehyde oxime **1d** (39 mg, 0.250 mmol) and maleimide **4a** (121 mg, 1.25 mmol) according to the general procedure afforded product **5d** (61 mg,

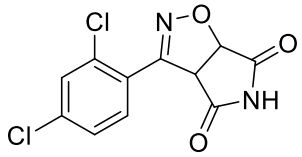
98%) as a white solid; light yellow plates (recrystallized from methanol); mp 192-194 °C; IR (neat) cm^{-1} 1746, 1351, 1200; ^1H NMR (500 MHz, CD_3OD): δ (ppm) 7.99 (t, J = 1.5 Hz, 1H), 7.91 (dt, J = 8.0, 1.5 Hz, 1H), 7.50-7.43 (m, 2H), 5.51 (d, J = 9.5 Hz, 1H), 5.01 (d, J = 9.5 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ (ppm) 174.0, 172.6, 152.5, 134.4, 130.3, 129.9, 129.4, 127.4, 126.0, 82.7, 55.8; HR-MS (ESI-negative ionization): calcd for $C_{11}H_7ClN_2O_3$ ($[M-H]^-$): 249.0067, found: 249.0077.

3-(2-Chlorophenyl)-3a,6a-dihydro-4*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*)-dione (**5e**)



Reaction of *o*-chlorobenzaldehyde oxime **1e** (39 mg, 0.250 mmol) and maleimide **4a** (121 mg, 1.25 mmol) according to the general procedure afforded product **5e** (55 mg, 87%) as a white solid; light yellow plates (recrystallized from methanol); mp 150.0-152.0 °C; IR (neat) cm^{-1} 1733, 1338, 1185; ^1H NMR (500 MHz, CD_3OD): δ (ppm) 7.56-7.51 (m, 2H), 7.47 (dt, J = 7.5, 1.5 Hz, 1H), 7.39 (dt, J = 7.5, 1.5 Hz, 1H), 5.53 (d, J = 9.5 Hz, 1H), 5.16 (d, J = 9.5 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ (ppm) 174.5, 172.2, 153.1, 132.8, 131.4, 131.2, 130.2, 126.9, 126.5, 81.9, 57.9; HR-MS (ESI-negative ionization): calcd for $C_{11}H_7ClN_2O_3$ ($[M-H]^-$): 249.0067, found: 249.0077.

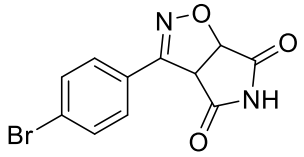
3-(2,4-Dichlorophenyl)-3a,6a-dihydro-4*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*)-dione (**5f**)



Reaction of 2,4-dichlorobenzaldehyde oxime **1f** (48 mg, 0.250 mmol) and maleimide **4a** (121 mg, 1.25 mmol) according to the general procedure afforded product **5f** (68 mg, 95%) as a light yellow solid; yellow plates (recrystallized from methanol); mp 175-177 °C; IR (neat) cm^{-1} 1734, 1336, 1187; ^1H NMR (500 MHz, CD_3OD): δ (ppm) 7.64-7.61 (m, 2H), 7.45 (dd, J = 9.0, 2.0 Hz, 1H), 5.56 (d, J = 9.5 Hz, 1H), 5.16 (d, J = 9.5 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ (ppm) 174.5, 172.5, 152.5, 136.9, 134.0, 132.6, 130.2,

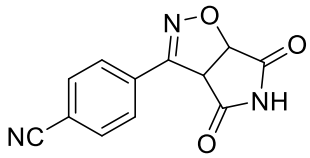
127.6, 125.6, 82.3, 57.9; HR-MS (ESI-negative ionization): calcd for $C_{11}H_6Cl_2N_2O_3$ ([M-H]$^-$): 282.9677, found: 282.9684.

3-(4-Bromophenyl)-3a,6a-dihydro-4*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*)-dione (**5g**)



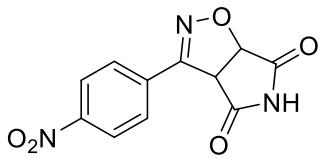
Reaction of *p*-bromobenzaldehyde oxime **1g** (50 mg, 0.250 mmol) and maleimide **4a** (121 mg, 1.25 mmol) according to the general procedure afforded product **5g** (63 mg, 85%) as a white solid; light yellow plates (recrystallized from methanol); mp 206.0-207.0 °C; IR (neat) cm^{-1} 1730, 1333, 1214; ^{1}H NMR (500 MHz, CD_3OD): δ (ppm) 7.87 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 8.5 Hz, 2H), 5.50 (d, J = 9.5 Hz, 1H), 5.00 (d, J = 9.5 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ (ppm) 174.4, 172.9, 153.0, 131.8, 129.6, 126.8, 124.9, 82.8, 56.1; HR-MS (ESI-negative ionization): calcd for $C_{11}H_7BrN_2O_3$ ([M-H]$^-$): 292.9562, found: 292.9558.

4-(4,6-Dioxo-3a,5,6,6a-tetrahydro-4*H*-pyrrolo[3,4-*d*]isoxazol-3-yl)benzonitrile (**5h**)



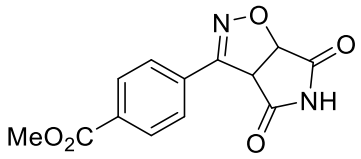
Reaction of *p*-cyanobenzaldehyde oxime **1h** (37 mg, 0.250 mmol) and maleimide **4a** (121 mg, 1.25 mmol) according to the general procedure afforded product **5h** (52 mg, 87%) as a white solid; white needles (recrystallized from methanol); mp 254-256 °C (dec); IR (neat) cm^{-1} 1732, 1339, 1217; ^{1}H NMR (500 MHz, CD_3OD/ DMSO-*d*6= 20:1): δ (ppm) 8.16 (d, J = 8.3 Hz, 2H), 7.89 (d, J = 8.3 Hz, 2H), 5.26 (d, J = 9.5 Hz, 1H), 5.13 (d, J = 9.5 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD/ DMSO-*d*6= 20:1): δ (ppm) 174.2, 173.3, 153.3, 132.8, 132.2, 128.9, 118.6, 113.9, 83.6, 56.1; HR-MS (ESI-negative ionization): calcd for $C_{12}H_7N_3O_3$ ([M-H]$^-$): 240.0409, found: 240.0419.

3-(4-Nitrophenyl)-3a,6a-dihydro-4*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*)-dione (**5i**)



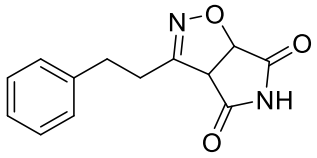
Reaction of *p*-nitrobenzaldehyde oxime **1i** (42 mg, 0.250 mmol) and maleimide **4a** (121 mg, 1.25 mmol) according to the general procedure afforded product **5i** (62 mg, 95%) as a light yellow solid; light yellow needles (recrystallized from methanol); mp 243-245 °C (dec); IR (neat) cm^{-1} 1733, 1340, 1214; ^{1}H NMR (500 MHz, DMSO-*d*6): δ (ppm) 11.96 (s, 1H), 8.32 (d, J = 9.0 Hz, 2H), 8.13 (d, J = 9.0 Hz, 2H), 5.60 (d, J = 9.3 Hz, 1H), 5.22 (d, J = 9.3 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-*d*6): δ (ppm) 174.7, 173.8, 153.4, 149.1, 134.0, 129.7, 124.5, 83.9, 56.5; HR-MS (ESI-negative ionization): calcd for $C_{11}H_7N_3O_5$ ([M-H]$^-$): 260.0307, found: 260.0314.

Methyl 4-(4,6-dioxo-3a,5,6,6a-tetrahydro-4*H*-pyrrolo[3,4-*d*]isoxazol-3-yl)benzoate (**5k**)



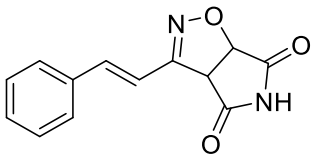
Reaction of *p*-methoxycarbonylbenzaldehyde oxime **1k** (45 mg, 0.250 mmol) and maleimide **4a** (121 mg, 1.25 mmol) according to the general procedure afforded **5k** (60 mg, 95%) as a white solid; colorless prisms (recrystallized from methanol); mp 211-212 °C; IR (neat) cm^{-1} 1730, 1355, 1279, 1198; ^{1}H NMR (500 MHz, CD_3OD/DMSO-*d*6= 20:1): δ (ppm) 8.10 (s, 4H), 5.59 (d, J = 9.5 Hz, 1H), 5.12 (d, J = 9.5 Hz, 1H), 3.95 (s, 3H) ; ^{13}C NMR (75 MHz, CD_3OD/ DMSO-*d*6= 20:1): δ (ppm) 174.2, 173.1, 166.4, 153.4, 132.0, 131.9, 129.6, 128.2, 83.2, 56.2, 52.0; HR-MS (ESI-negative ionization): calcd for $C_{13}H_{10}N_2O_5$ ([M-H]$^-$): 273.0511, found: 273.0522.

3-Phenethyl-3a,6a-dihydro-4*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*)-dione (**5l**)



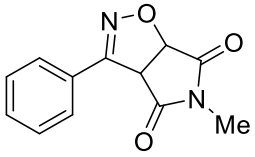
Reaction of 3-phenylpropylaldehyde oxime **1l** (37 mg, 0.250 mmol) and maleimide **4a** (121 mg, 1.25 mmol) according to the general procedure afforded product **5l** (19 mg, 31%) as a light yellow solid; colorless needles (recrystallized from methanol); IR (neat) cm^{-1} 1733, 1340, 1187; ^1H NMR (500 MHz, CD_3OD): δ (ppm) 7.30-7.17 (m, 5H), 5.26 (d, J = 9.5 Hz, 1H), 4.40 (d, J = 9.5 Hz, 1H), 3.05-2.99 (m, 1H), 2.96-2.90 (m, 1H), 2.86-2.79 (m, 1H), 2.75-2.69 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ (ppm) 175.2, 173.2, 155.1, 140.5, 128.4, 128.2, 126.2, 80.7, 58.5, 31.7, 27.9; HR-MS (ESI-negative ionization): calcd for $C_{13}H_{12}N_2O_3$ ([M-H]$^-$): 243.0770, found: 243.0769.

(*E*)-3-Styryl-3a,6a-dihydro-4*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*)-dione (**5m**)



Reaction of cinnamaldehyde oxime **1m** (18 mg, 0.125 mmol) and maleimide **4a** (60 mg, 0.625 mmol) according to the general procedure afforded product **5m** (21 mg, 70%) as a white solid; white prisms (recrystallized from methanol); mp 266-268 °C (dec); IR (neat) cm^{-1} 1730, 1357, 1210; ^1H NMR (500 MHz, CD_3OD/ DMSO-*d*6= 20:1): δ (ppm) 7.64 (d, J = 8.5 Hz, 2H), 7.56 (d, J = 16.8 Hz, 1H), 7.46-7.44 (m, 2H), 7.41 (t, J = 7.0 Hz, 2H), 7.11 (d, J = 16.8 Hz, 1H), 5.48 (d, J = 9.0 Hz, 1H), 4.90 (d, J = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ (ppm) 174.5, 173.3, 154.7, 140.5, 136.1, 129.6, 129.2, 127.5, 115.2, 82.7, 55.8; HR-MS (ESI-negative ionization): calcd for $C_{13}H_{10}N_2O_3$ ([M-H]$^-$): 241.0613, found: 241.0626.

5-Methyl-3-phenyl-3a,6a-dihydro-4*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*)-dione (**5n**)



Reaction of benzaldoxime **1a** (30 mg, 0.250 mmol) and *N*-methyl maleimide **4b** (139 mg, 1.25 mmol) according to the general procedure afforded product **5m** (41 mg, 72%) as an orange solid; orange plates (recrystallized from methanol); mp 158-159 °C; IR (neat)

cm^{-1} 1717, 1369, 1210; ^{1}H NMR (500 MHz, CD_3OD/ DMSO-*d*6= 20:1): δ (ppm) 8.00 - 7.99 (m, 2H), 7.52 - 7.49 (m, 3H), 5.57 (d, *J* = 9.5 Hz, 1H), 5.12 (d, *J* = 9.5 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD/ DMSO-*d*6= 20:1): δ (ppm) 173.3, 172.2, 153.7, 131.0, 128.9, 128.2, 127.8, 81.5, 55.4.

5. CONCLUSIONS AND RECOMMENDATIONS

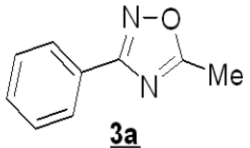
We developed a simple strategy to prepare in total nineteen 1,2,4-oxadiazoles and thirteen pyrrolo-isoxazoles through hypervalent iodine-assisted cyclization of benzaldoximes with corresponding dipolarophiles (nitriles or maleimides). In this procedure, *m*-CPBA and TfOH were used in stoichiometric amounts as terminal oxidant and ligand resource, respectively, to convert the pre-catalyst 2-iodobenzoic acid into the active hypervalent iodine species whose pseudo-cyclic structure was determined as the triflate salt of hydroxy(aryl)iodonium (IBA-OTf) in the crystal lattice. Further study on reaction mechanism showed that the cyclization undergoes via the formation of nitrile oxide intermediates whose stability in reaction solution governs their reactivity to the cycloaddition with a given dipolarophile. In the agreement with the frontier molecular orbital theory, both substrates bearing electron-withdrawing and electron-donating substituents reacted smoothly with nitriles or maleimides to afford 1,2,4-oxadiazoles or pyrrolo-isoxazoles in good to excellent yields. However, for those containing functional groups susceptible to hydrolysis or oxidation, the side reactions can compete against the desired cyclization to generate unwanted by-products and lower the isolated yield of expected cycloadducts.

The identity of all compounds was authenticated by ^{1}H NMR and ^{13}C NMR. IR and HR-MS were additionally recorded for new compounds. Especially, single X-ray diffraction was used to confirm the bicyclic structure of a typical pyrrolo-isoxazoles. Furthermore, structural characterization of different possible cationic hypervalent iodine species in the reaction solution was also conducted with the help of ESI-MS and NMR techniques to support the study on reaction mechanism.

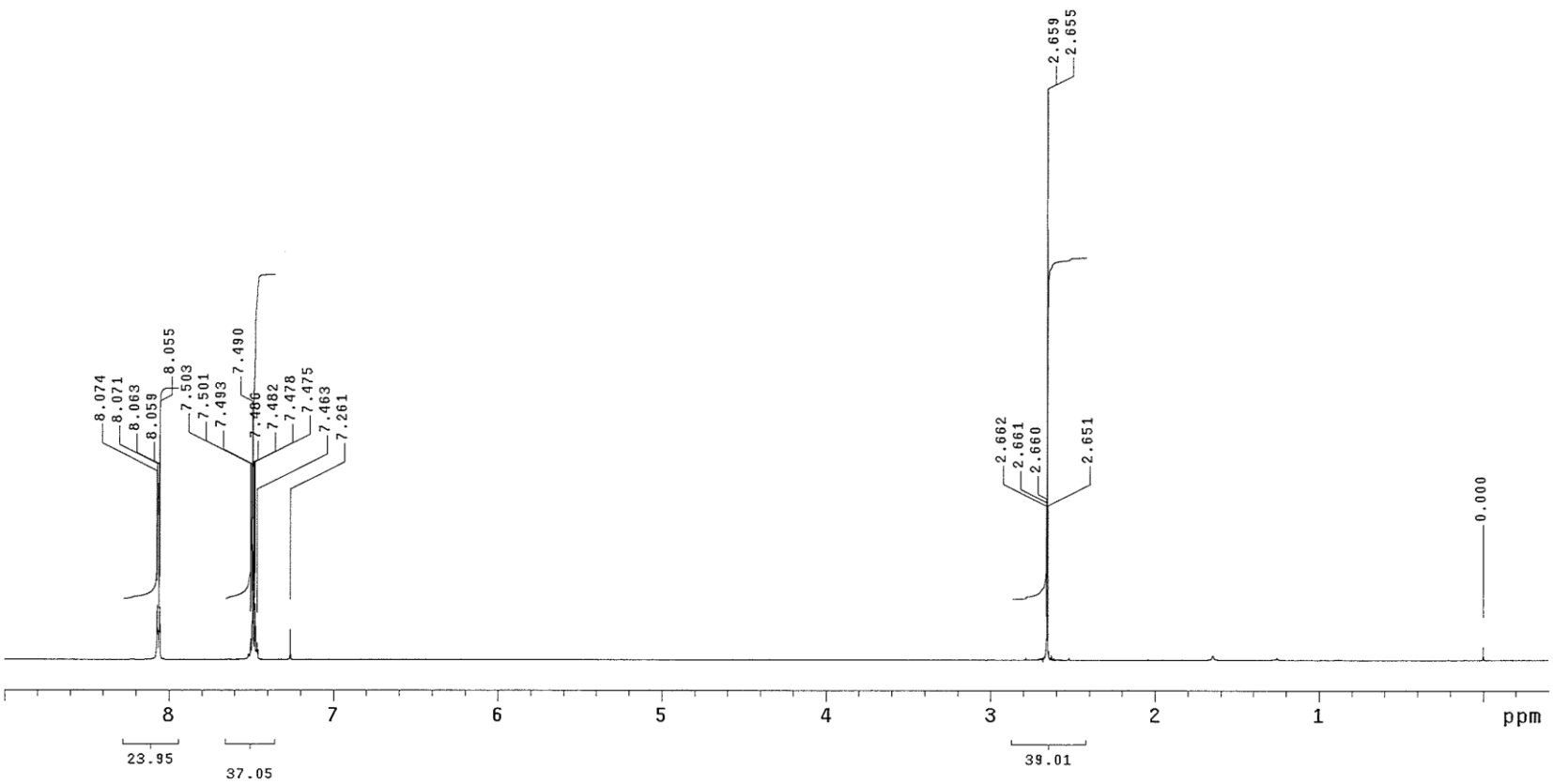
For future research, pericyclic cycloaddition to different dipolarophiles containing unsaturated carbon-carbon and carbon-heteroatom bonds (C≡C, C=N, C=S, C=O, etc.) should be studied to evaluate the catalytic activity and synthetic versatility of *in situ* generated IBA-OTf as well as to develop new methods for the synthesis of important heterocyclic scaffolds.

6. APPENDICES

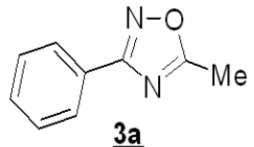
^{1}H NMR (500 MHz, $CDCl_3$)



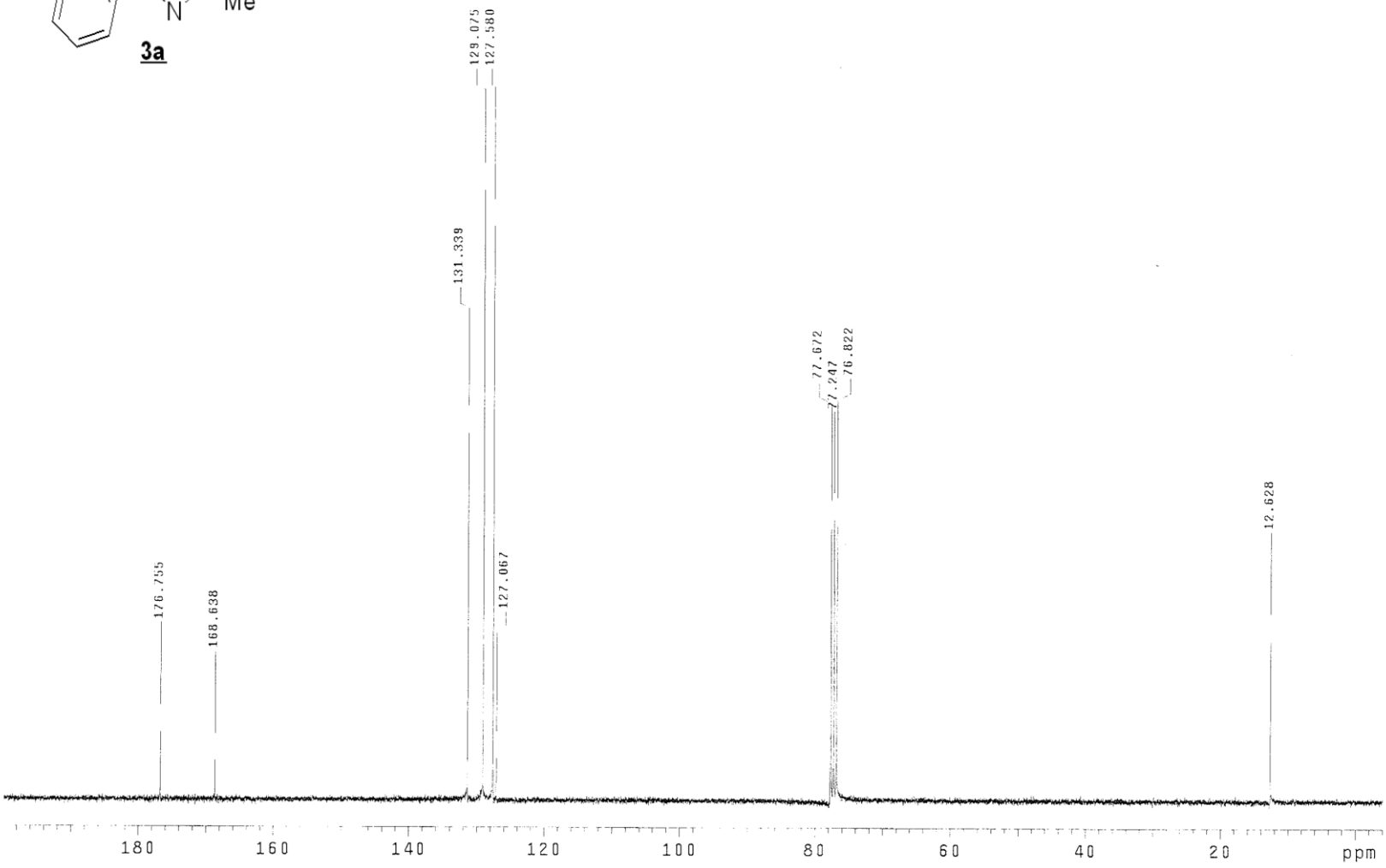
3a



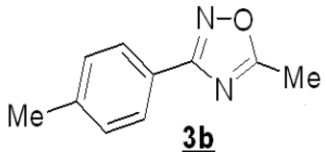
^{13}C NMR (75 MHz, $CDCl_3$)



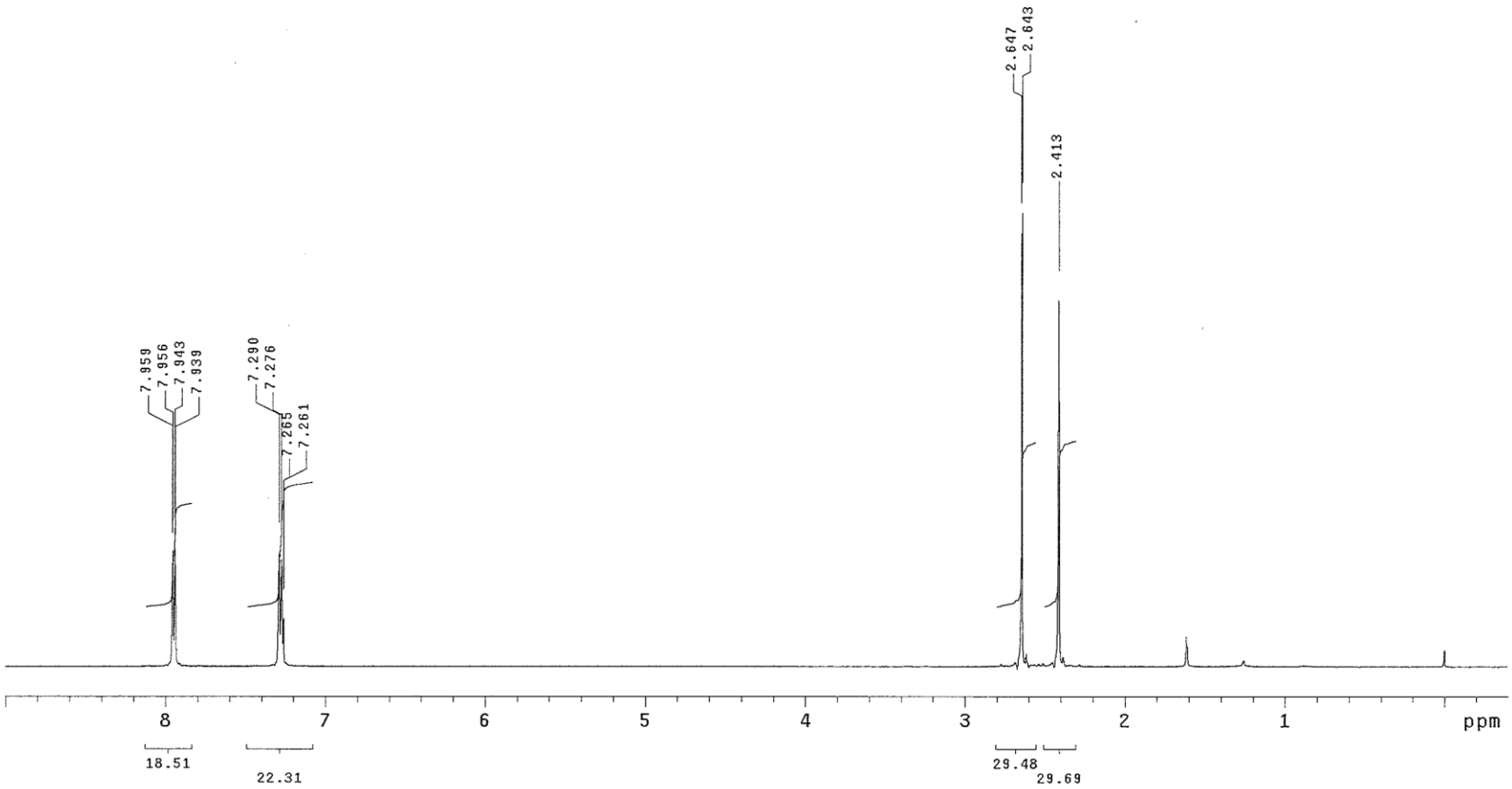
3a



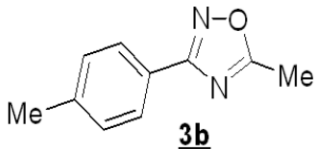
^{1}H NMR (500 MHz, $CDCl_3$)



3b

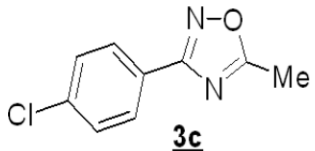


^{13}C NMR (75 MHz, $CDCl_3$)



3b

^{1}H NMR (500 MHz, $CDCl_3$)



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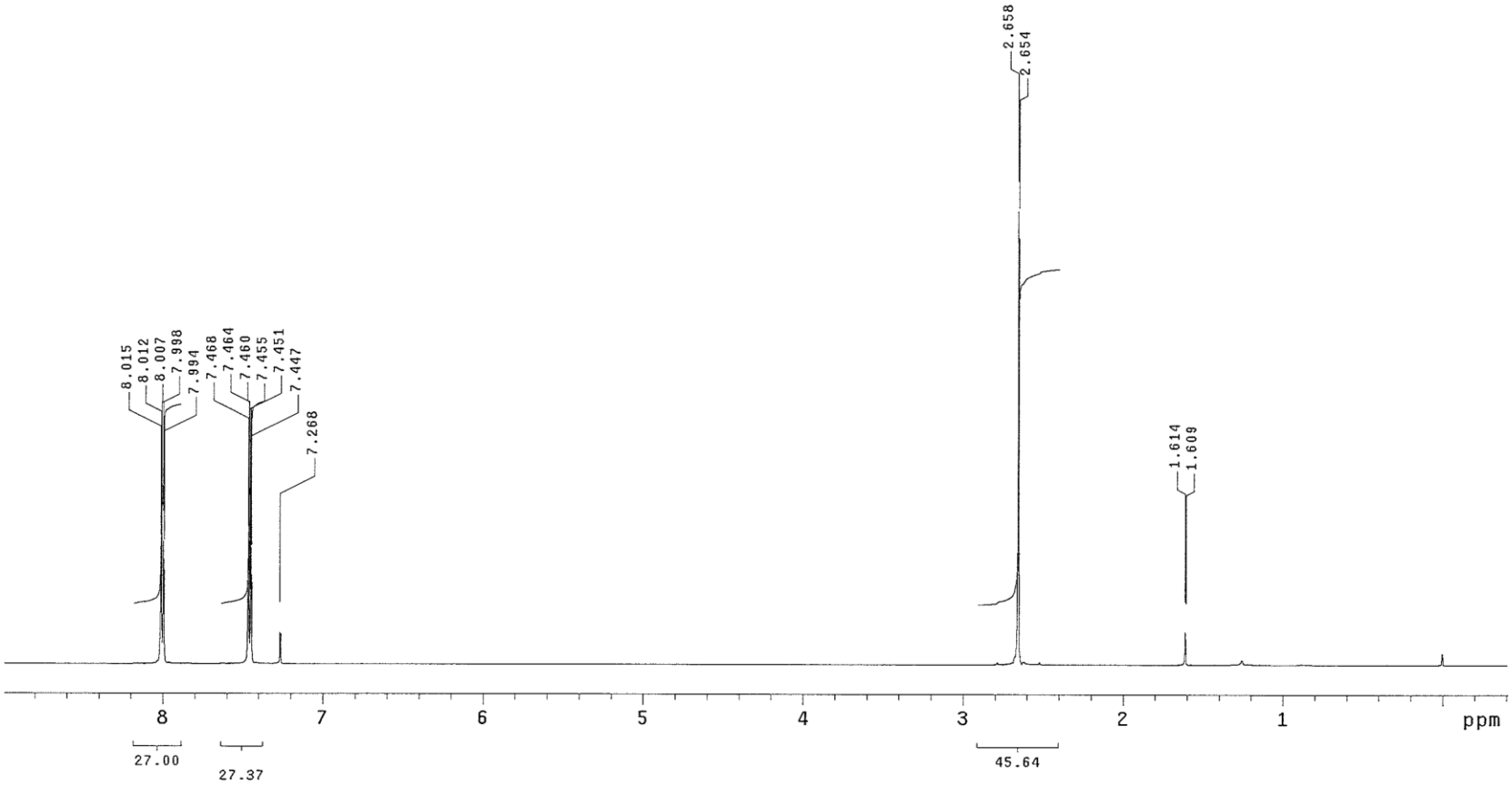

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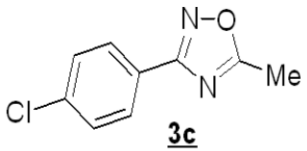

3c

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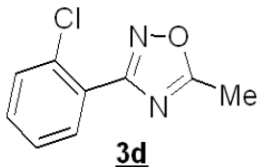

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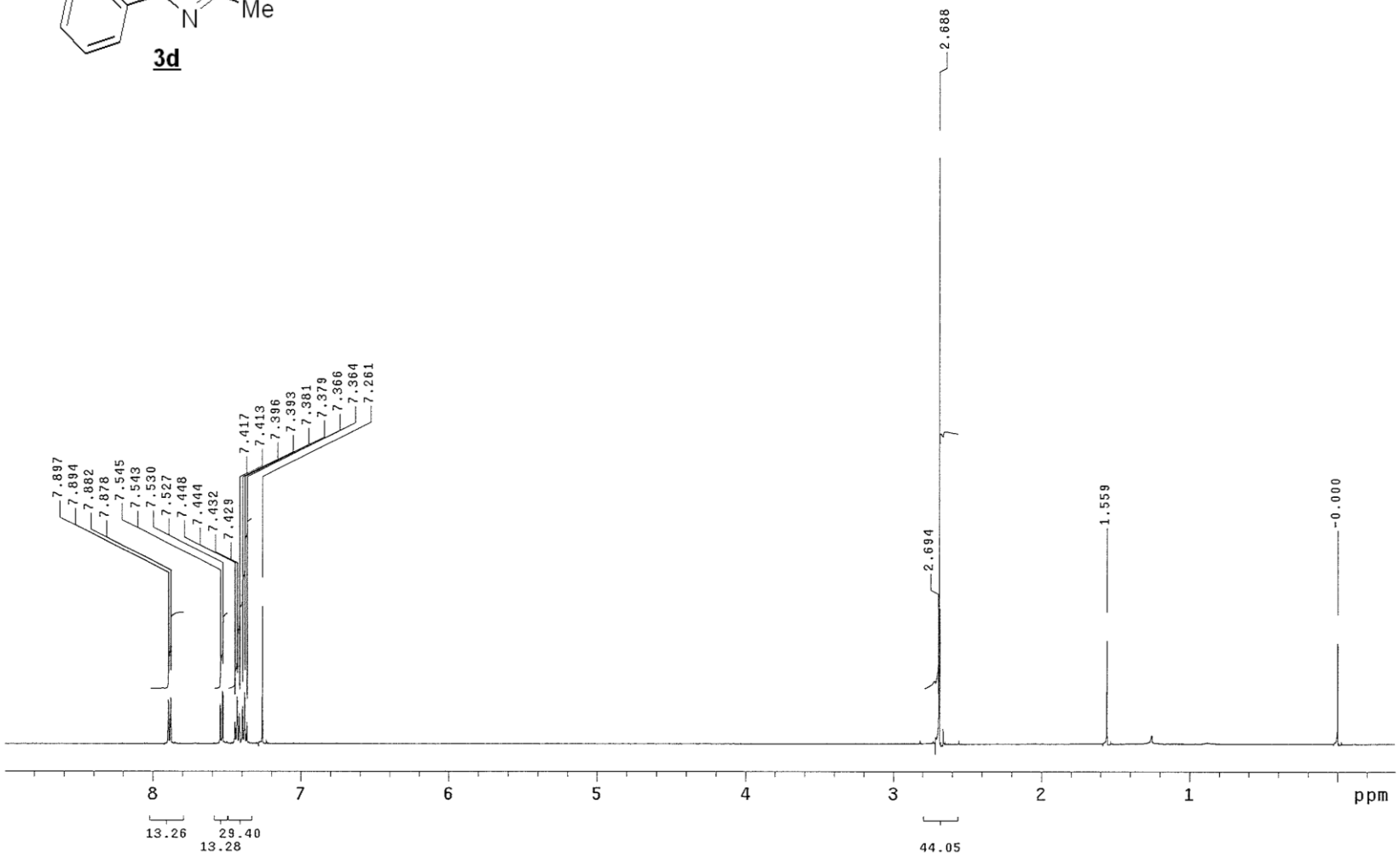

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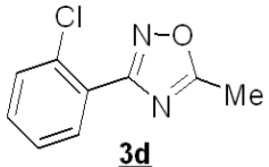

3d

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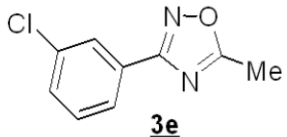

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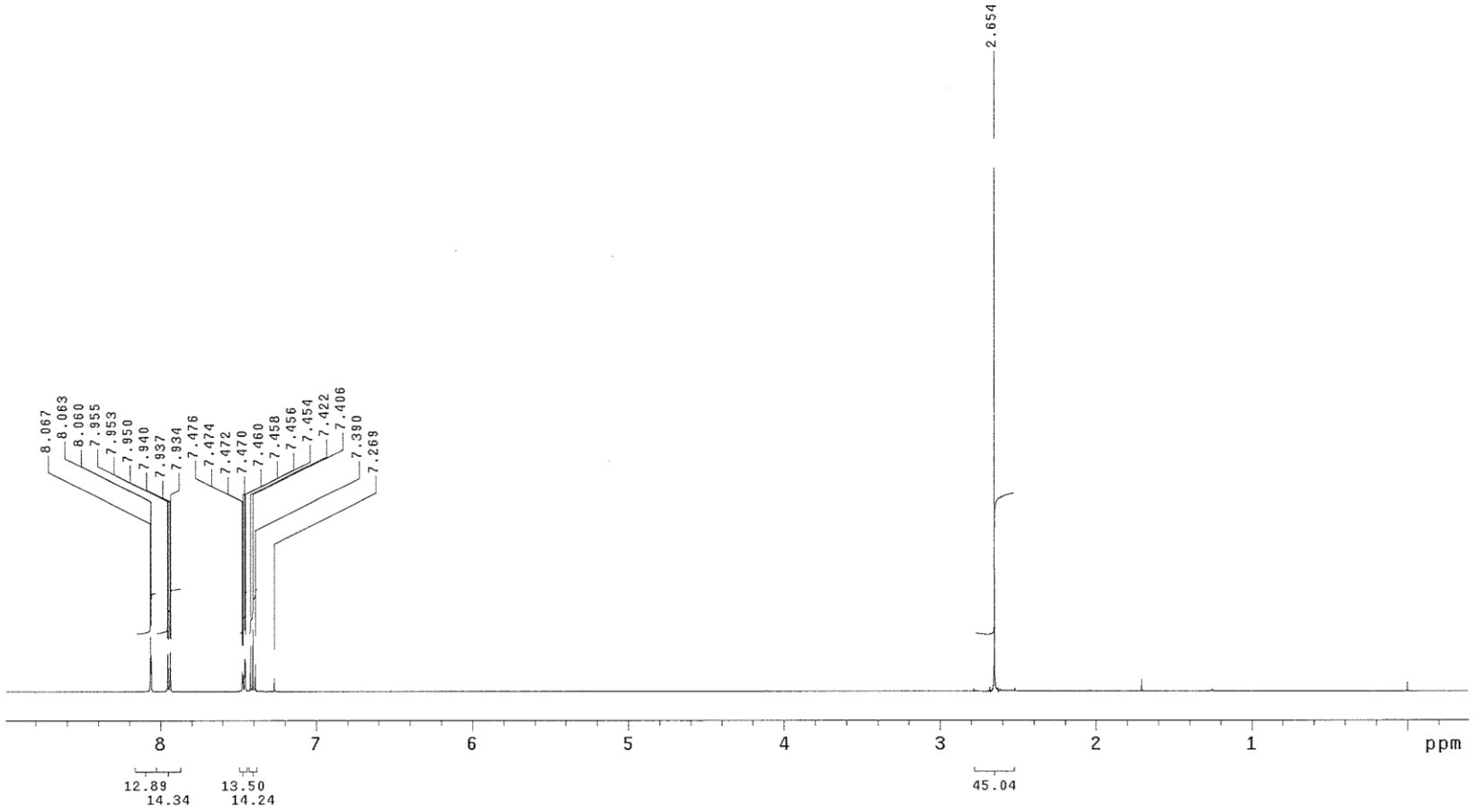

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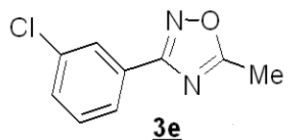

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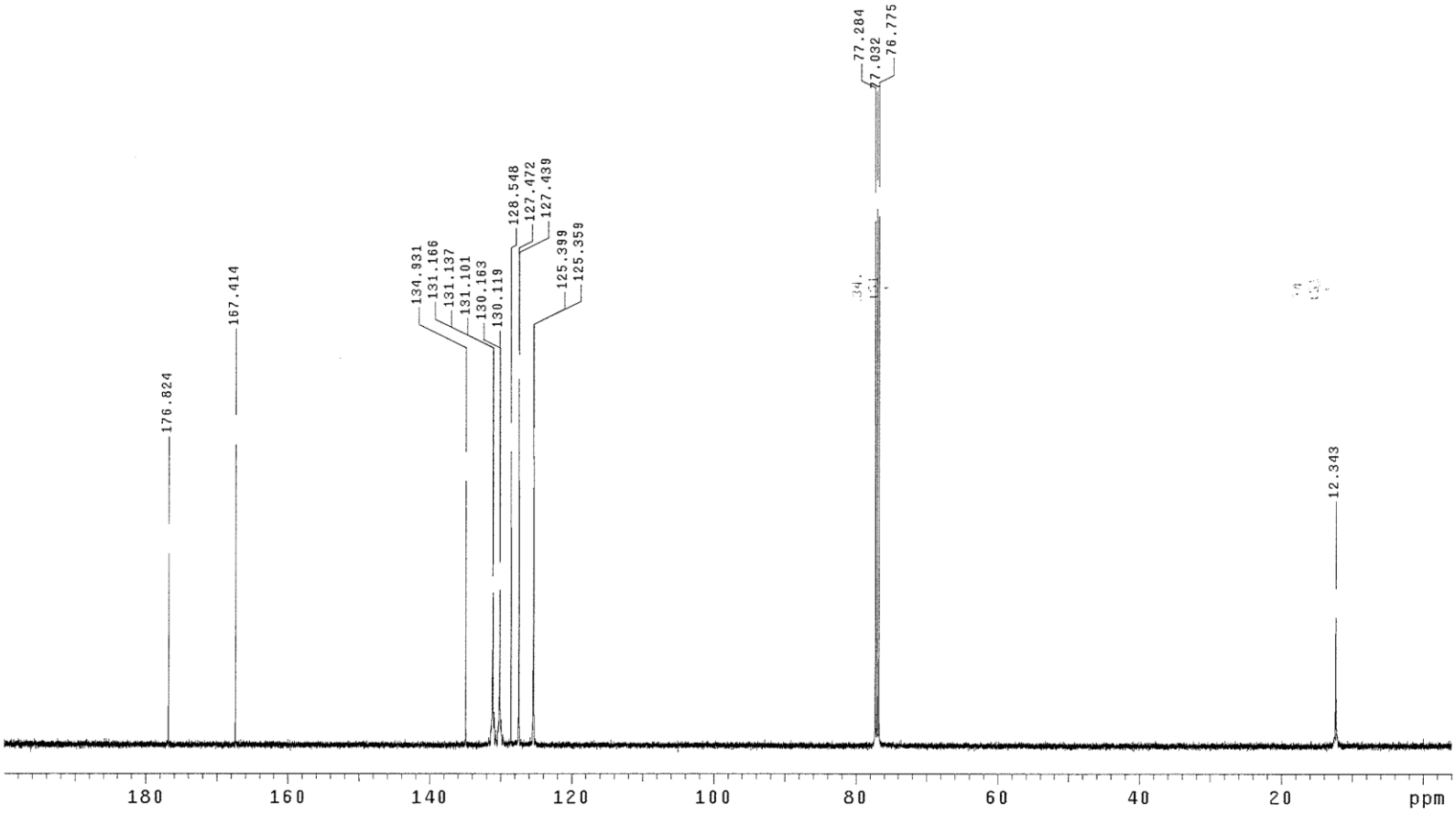

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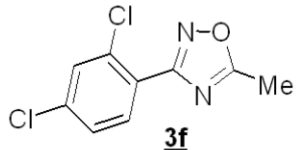

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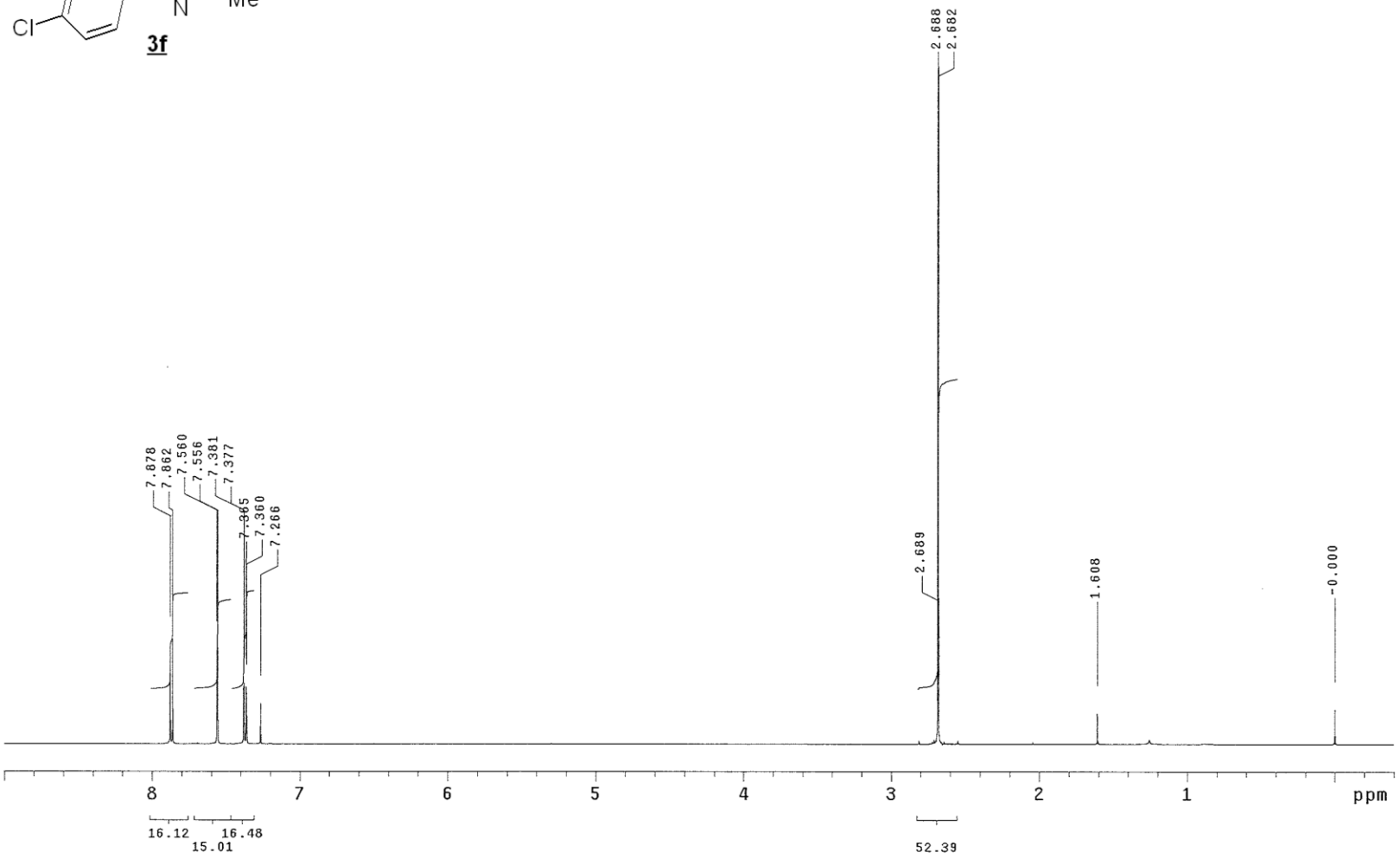

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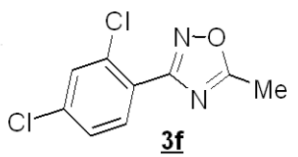
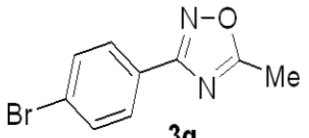


3f

^{1}H NMR (500 MHz, $CDCl_3$)



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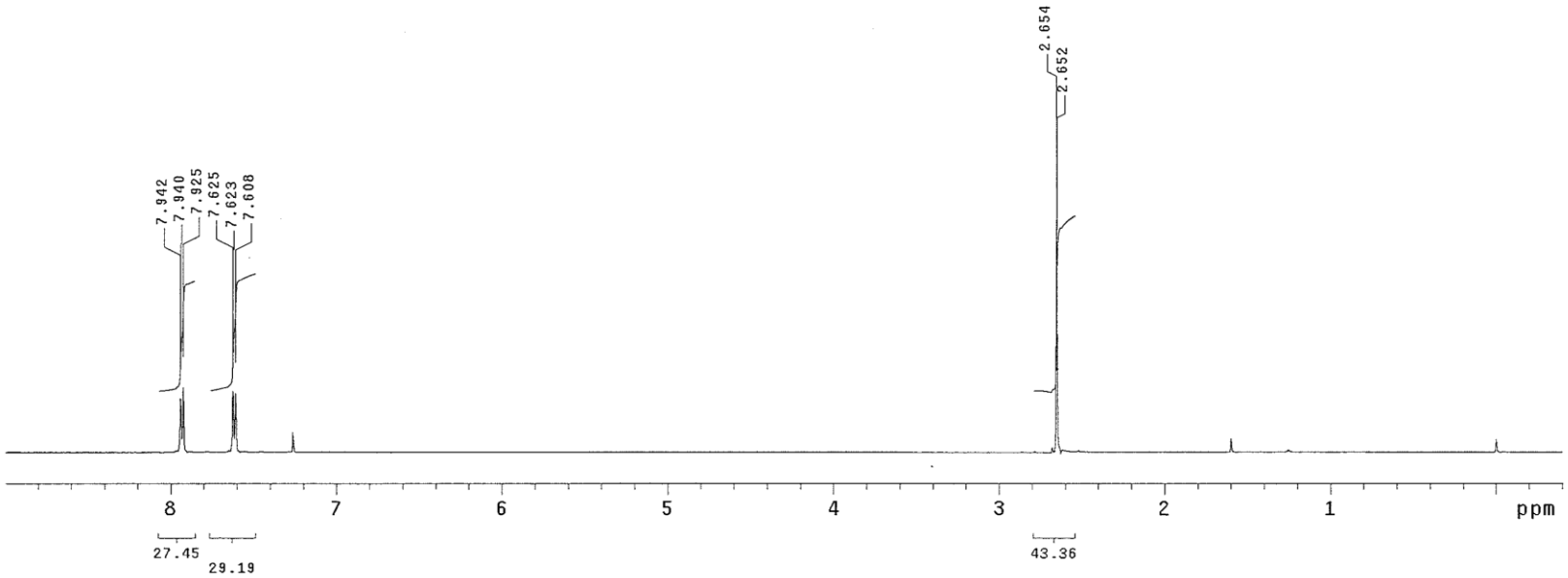

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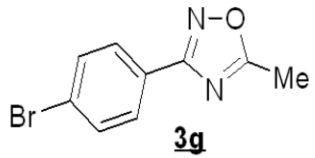

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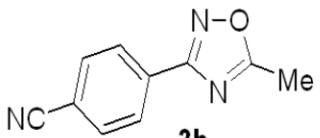

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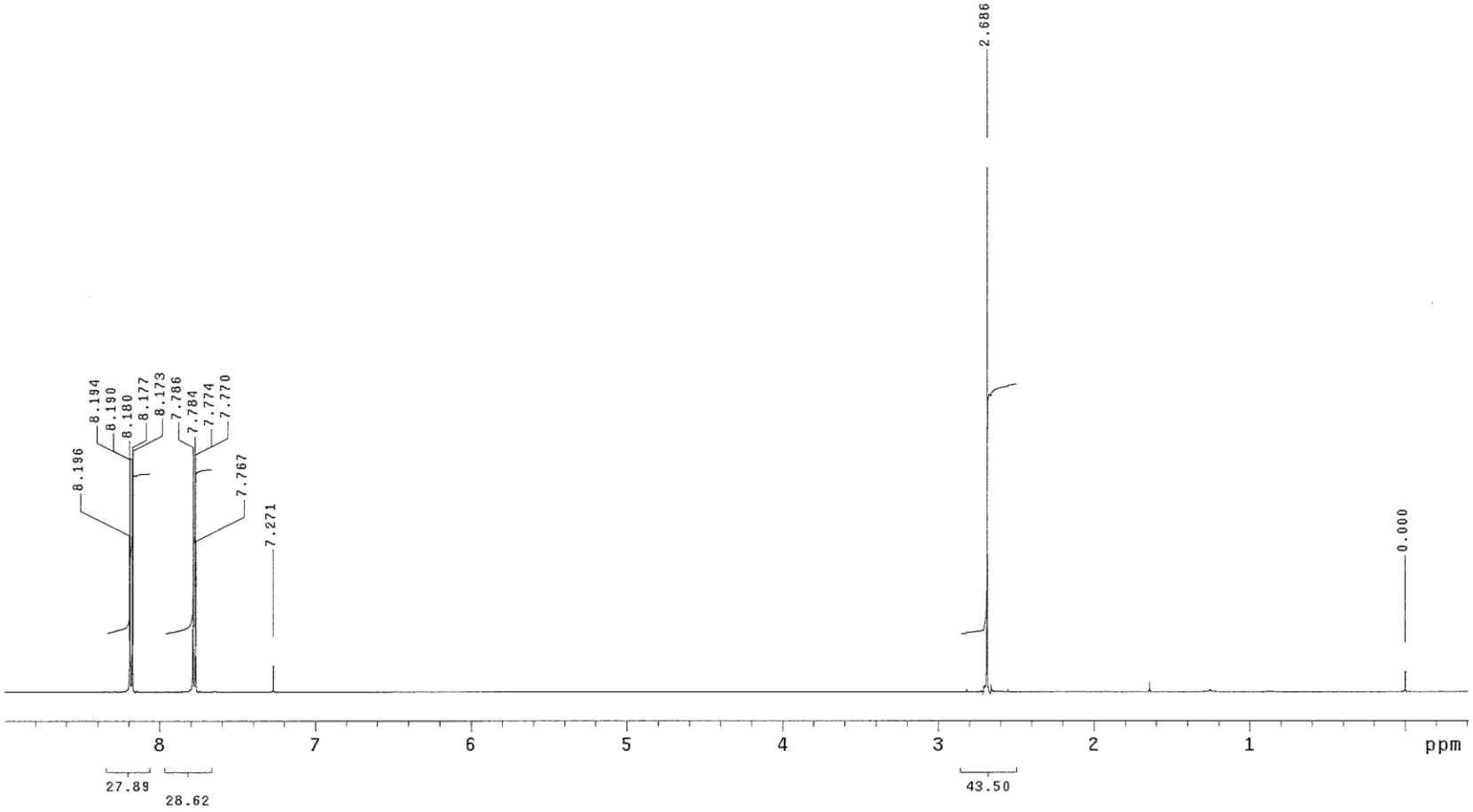
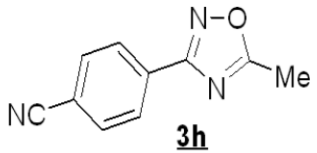
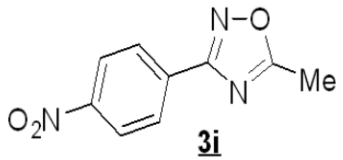


^{13}C NMR (75 MHz, $CDCl_3$)

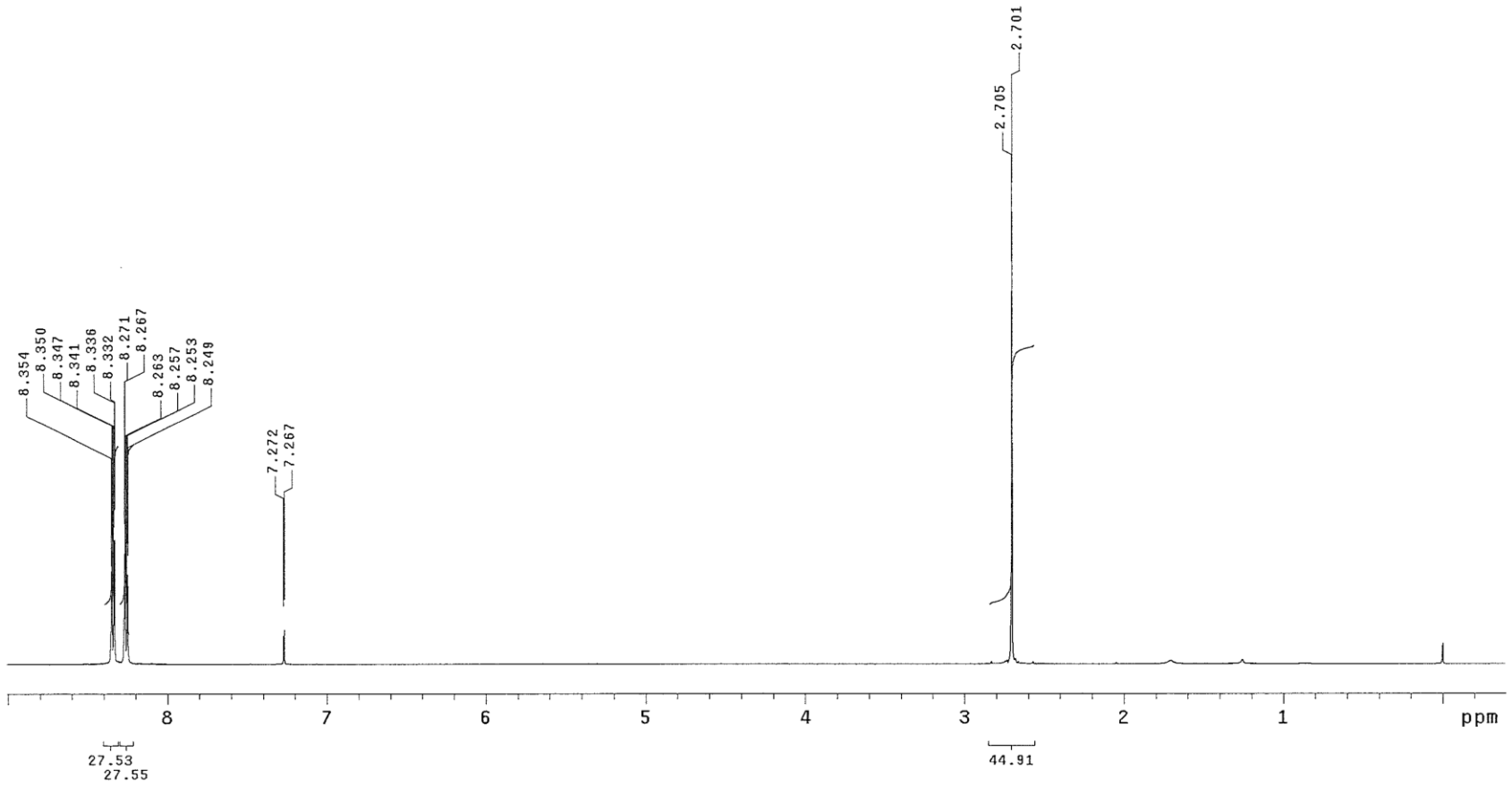


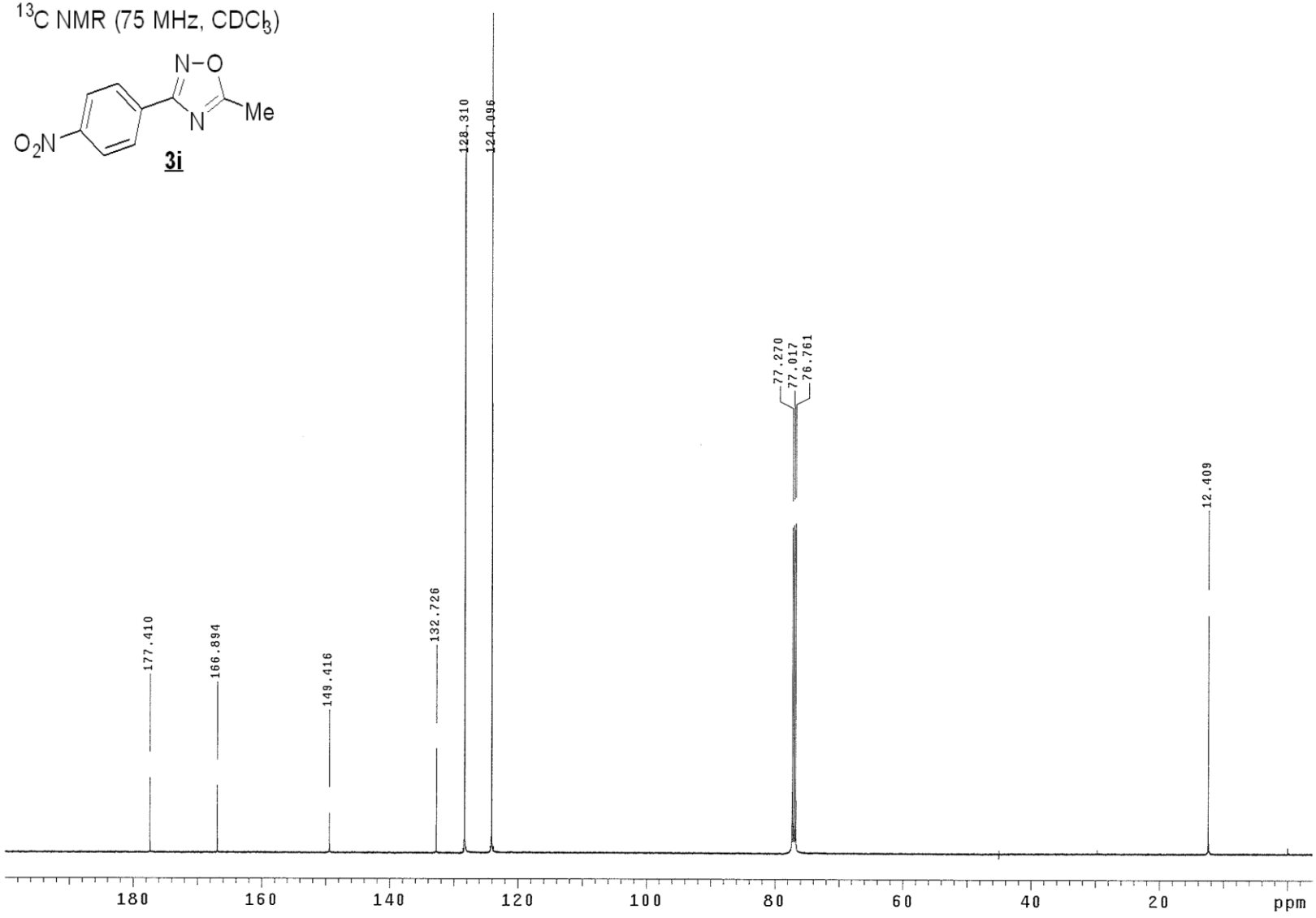
3h

^{1}H NMR (500 MHz, $CDCl_3$)

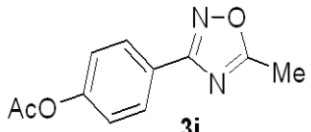


3i

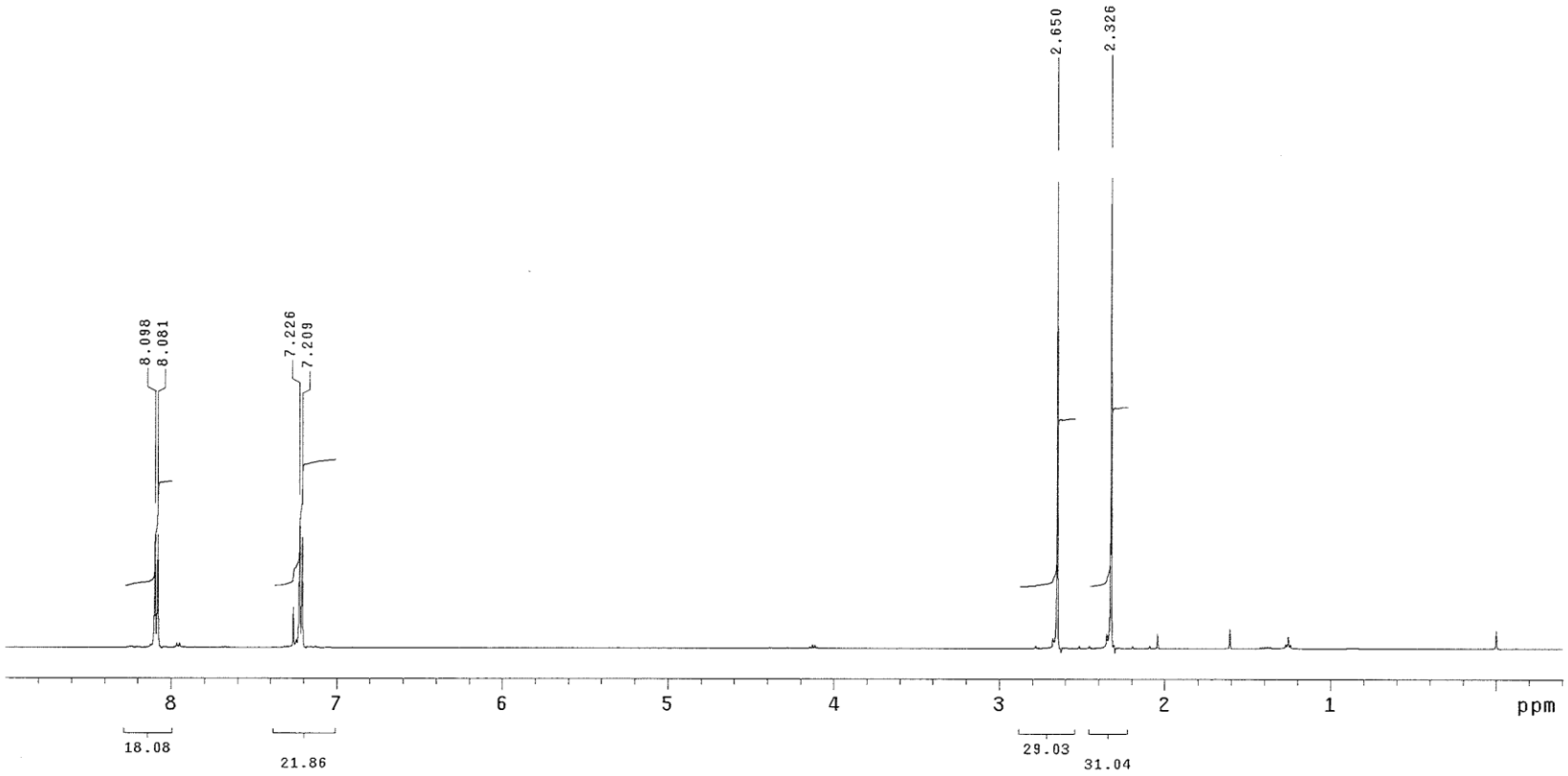



13C NMR (75 MHz, CDCl3)
N–O
N
Me
O2N
3i
177.410
166.894
149.416
132.726
128.310
124.096
77.270
77.017
76.761
12.409
180
160
140
120
100
80
60
40
20
ppm

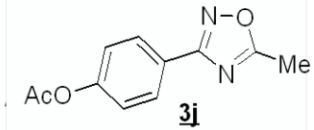
^{1}H NMR (500 MHz, $CDCl_3$)



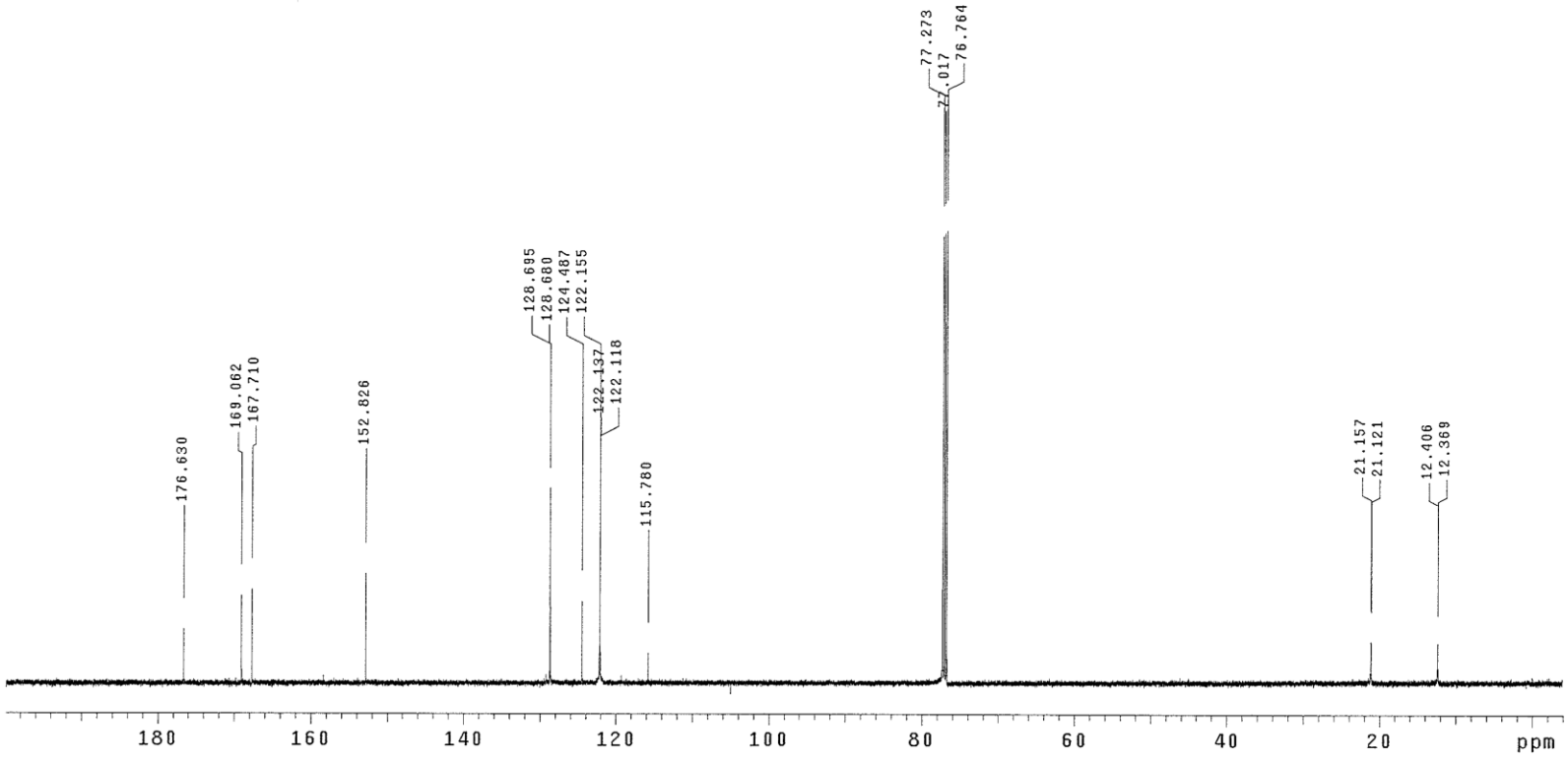
3j



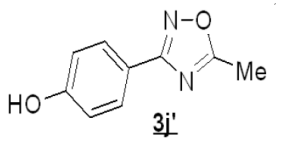
^{13}C NMR (75 MHz, $CDCl_3$)



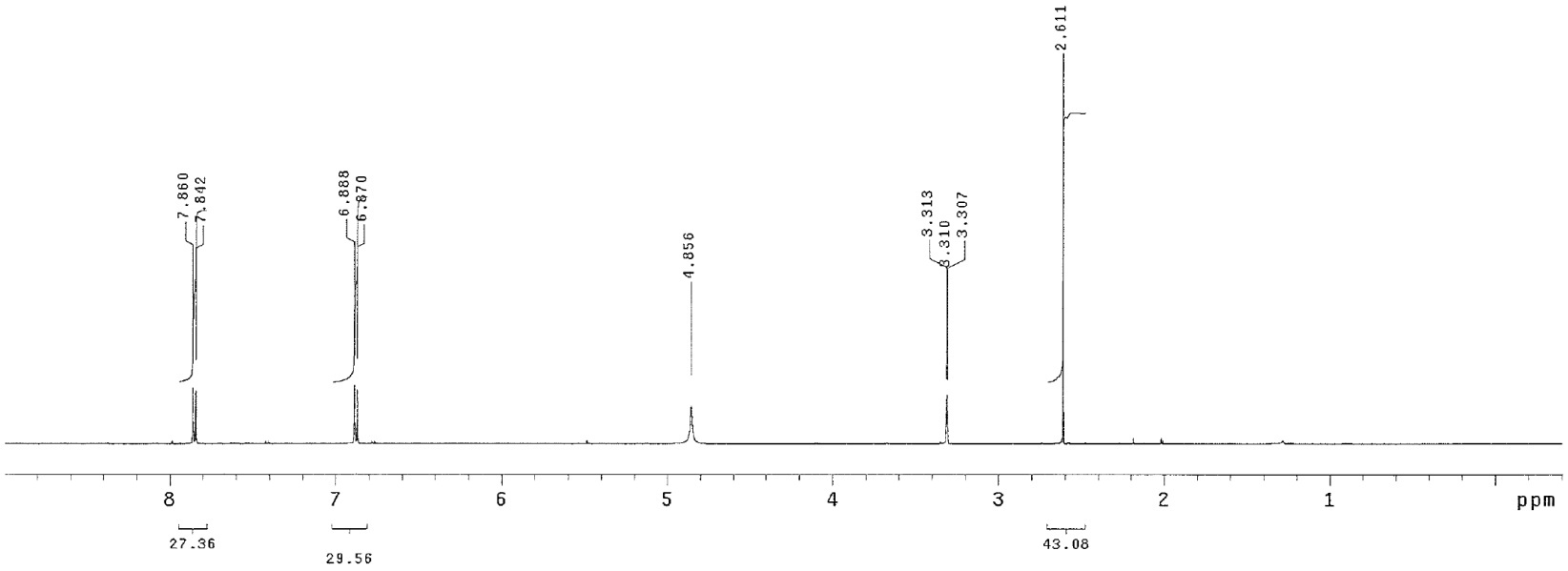
3j



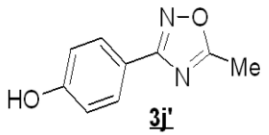
^{1}H NMR (500 MHz, CD_3OD)



3j'

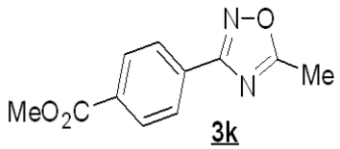


^{13}C NMR (75 MHz, CD_3OD)

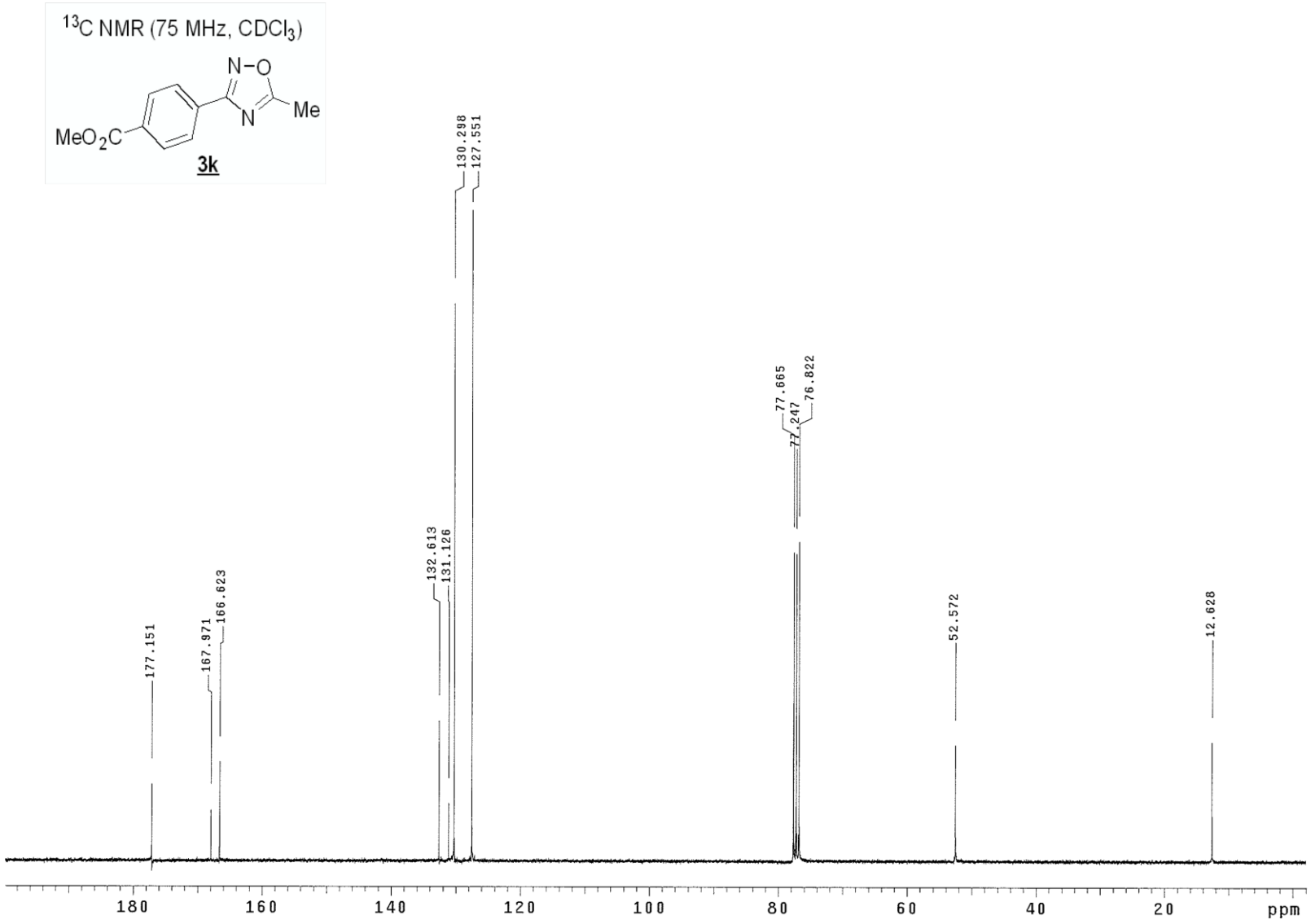


3j'

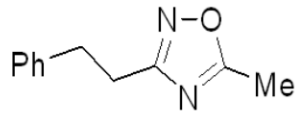
^{1}H NMR (500 MHz, $CDCl_3$)



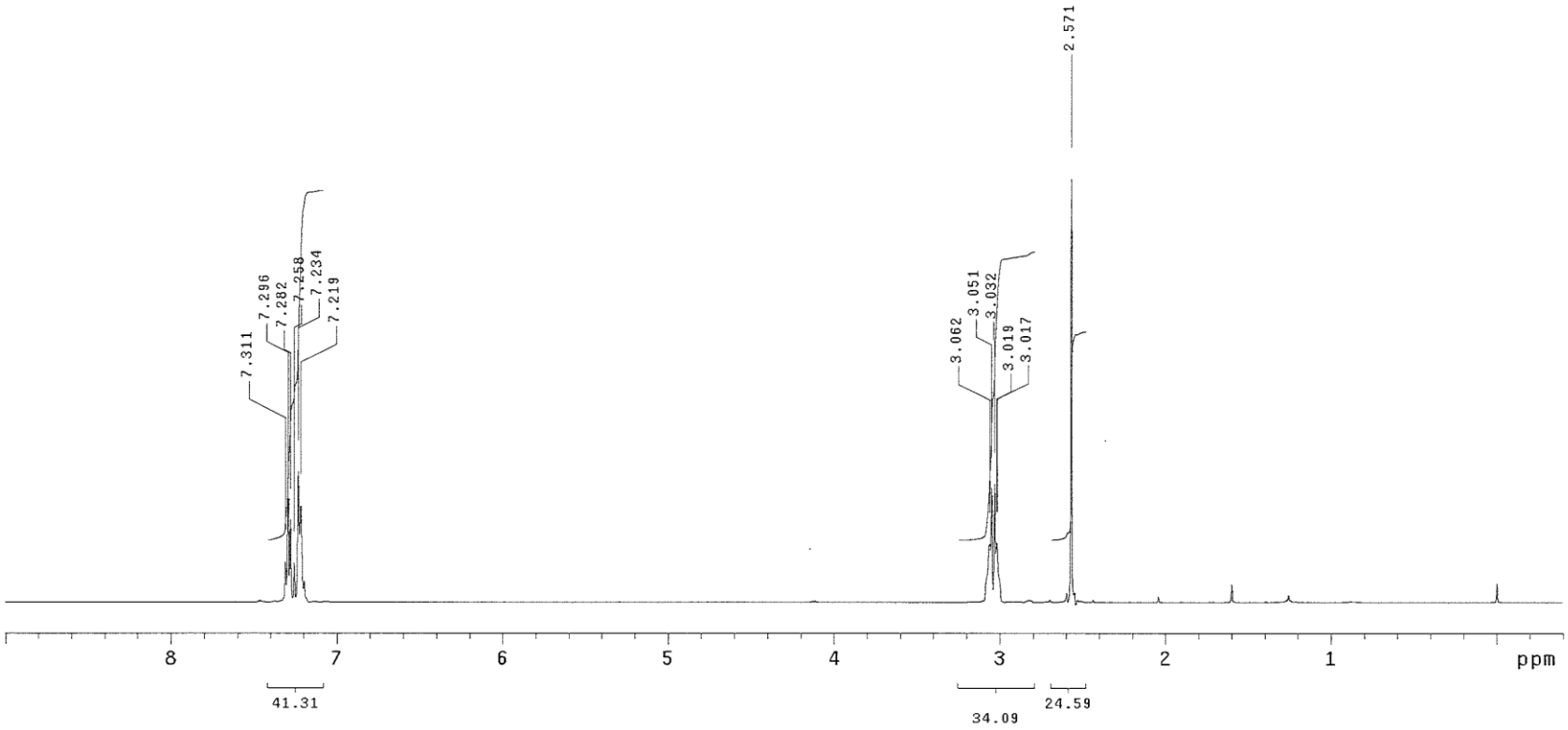
3k


^{13}C NMR (75 MHz, $CDCl_3$)
N–O
N
Me
MeO_2C
3k
177.151
167.971
166.623
132.613
131.126
130.298
127.551
77.665
77.247
76.822
52.572
12.628
180
160
140
120
100
80
60
40
20
ppm

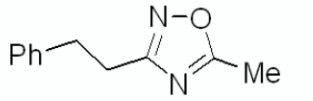
^{1}H NMR (500 MHz, $CDCl_3$)



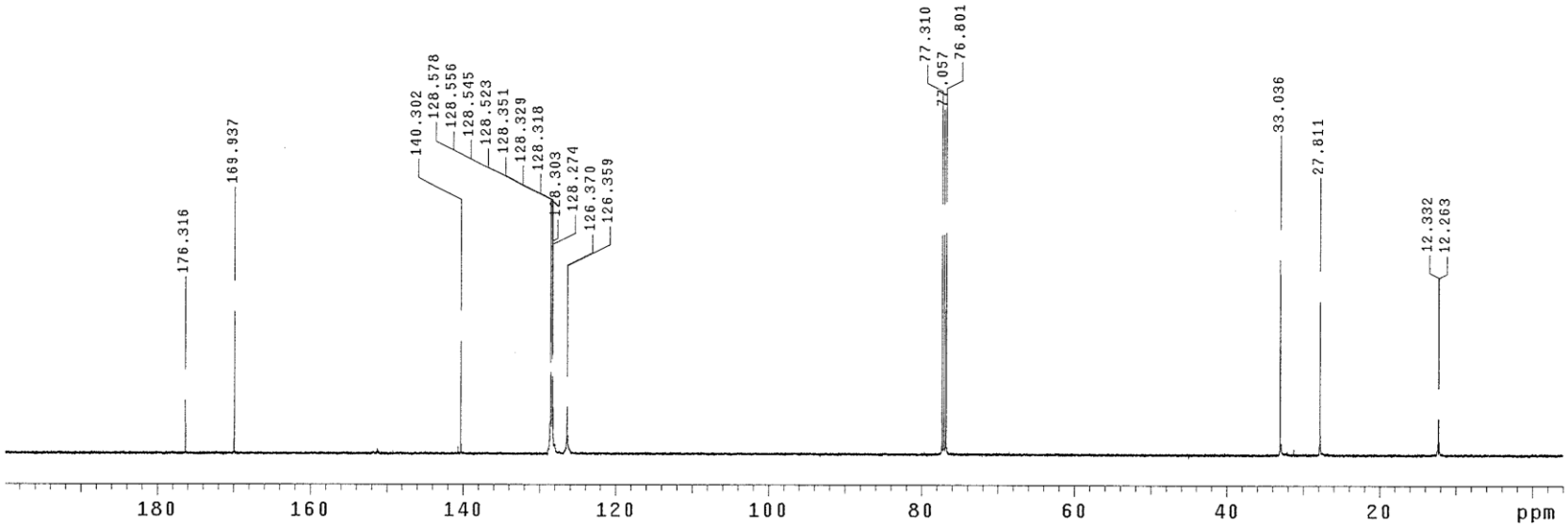
3l



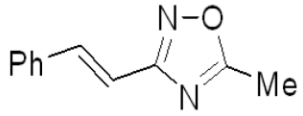
^{13}C NMR (75 MHz, $CDCl_3$)



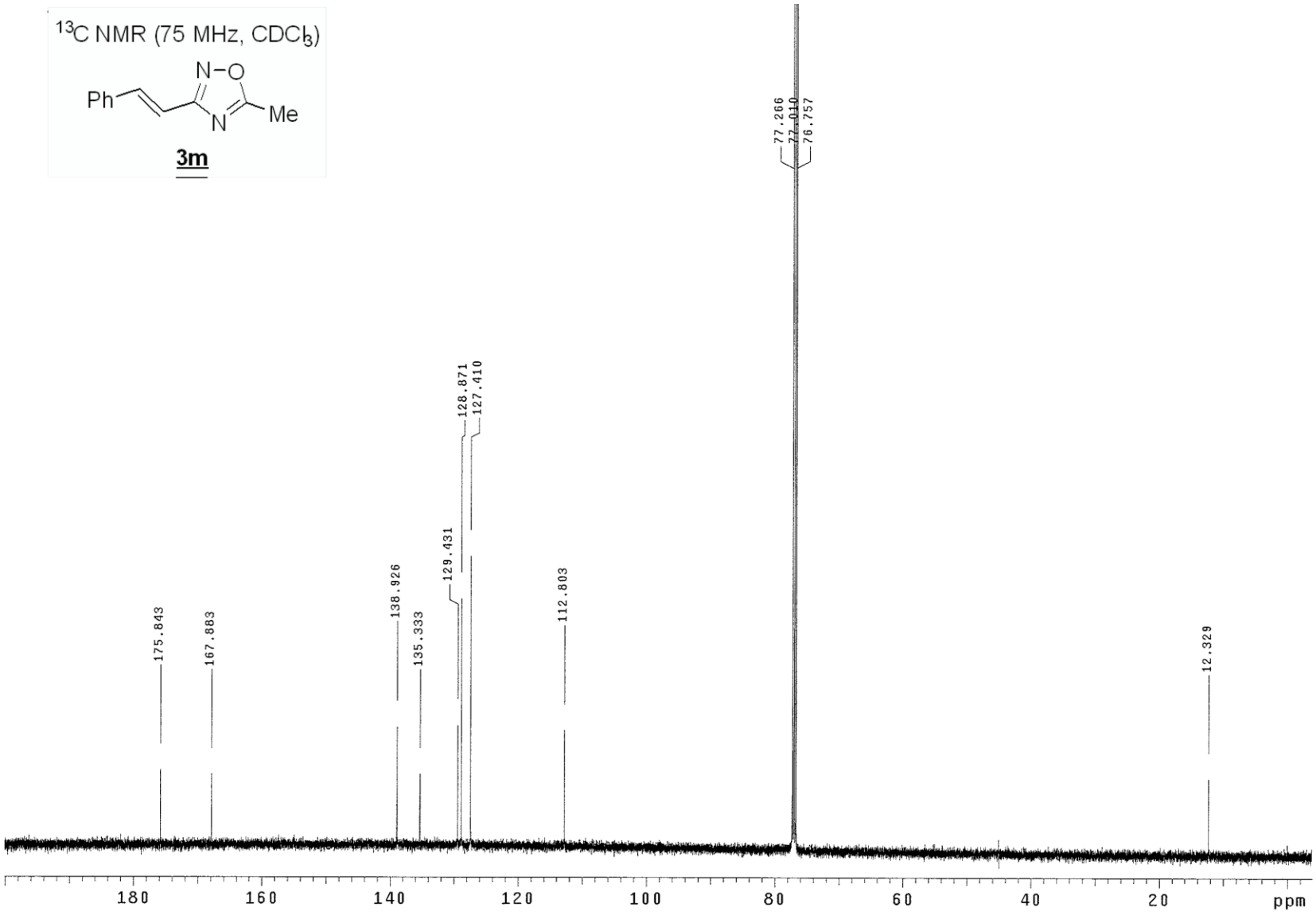
3l



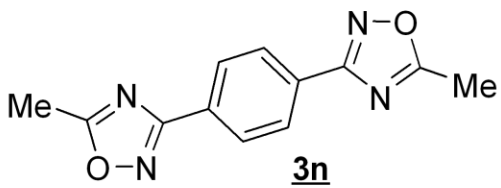
^{1}H NMR (500 MHz, $CDCl_3$)



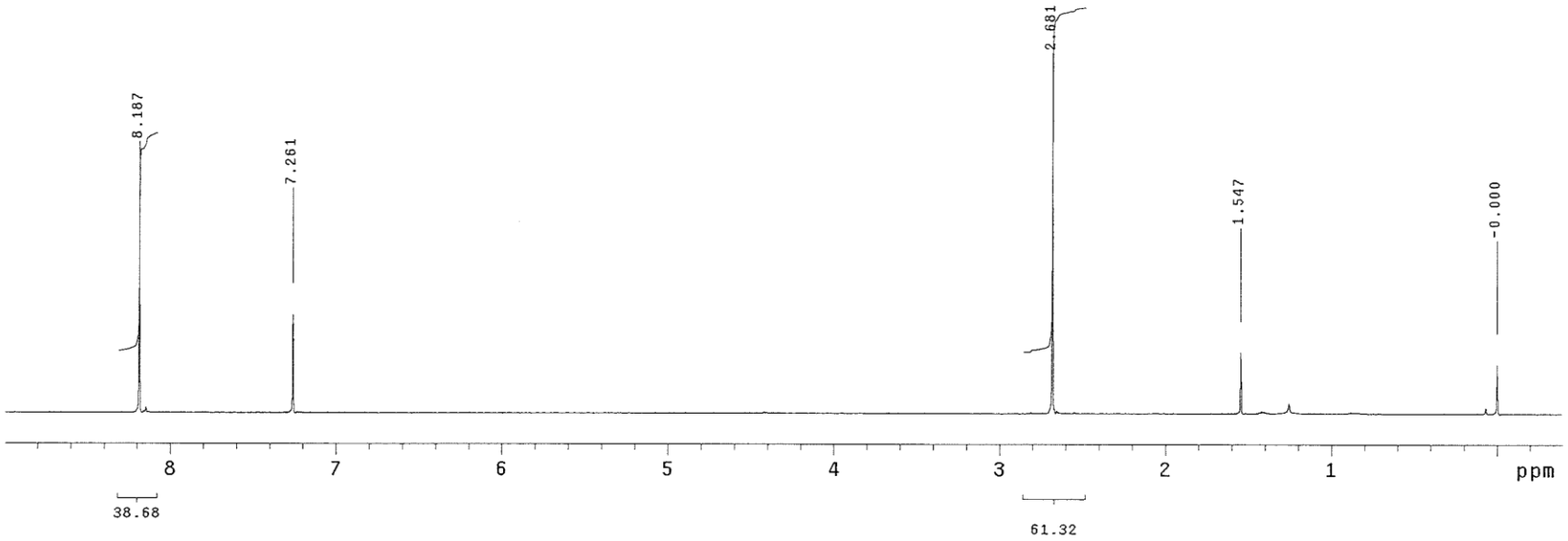
3m


13C NMR (75 MHz, CDCl3)
N–O
Ph
N
Me
3m
175.843
167.883
138.926
135.333
129.431
128.871
127.410
112.803
77.266
77.010
76.757
12.329
180
160
140
120
100
80
60
40
20
ppm

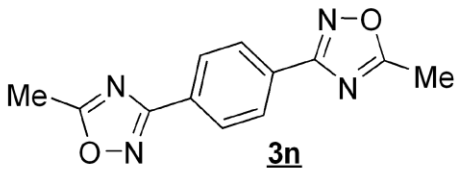
^{1}H NMR (500 MHz, $CDCl_3$)



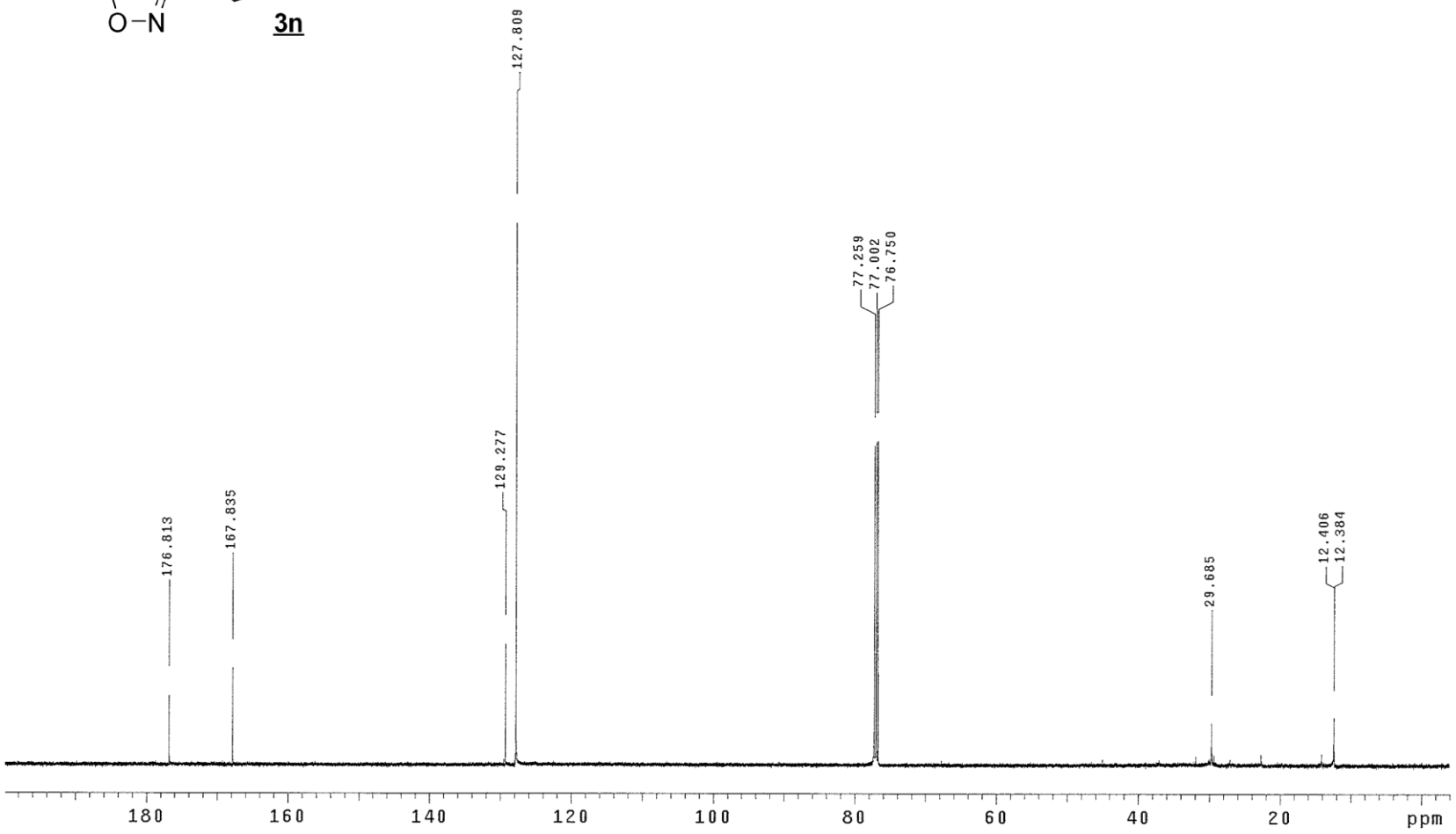
3n



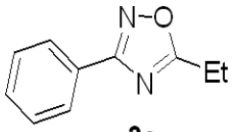
^{13}C NMR (75 MHz, $CDCl_3$)



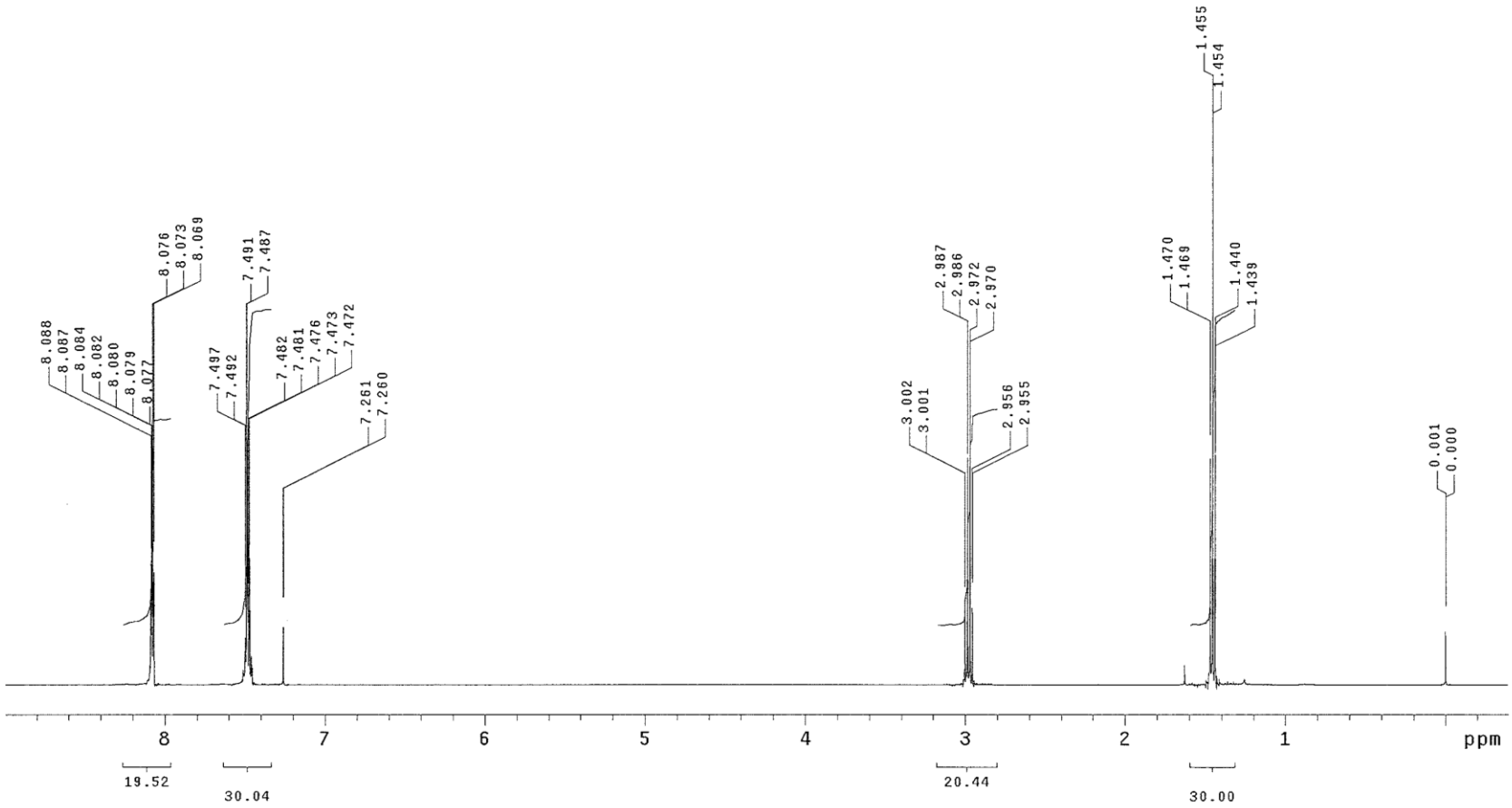
3n

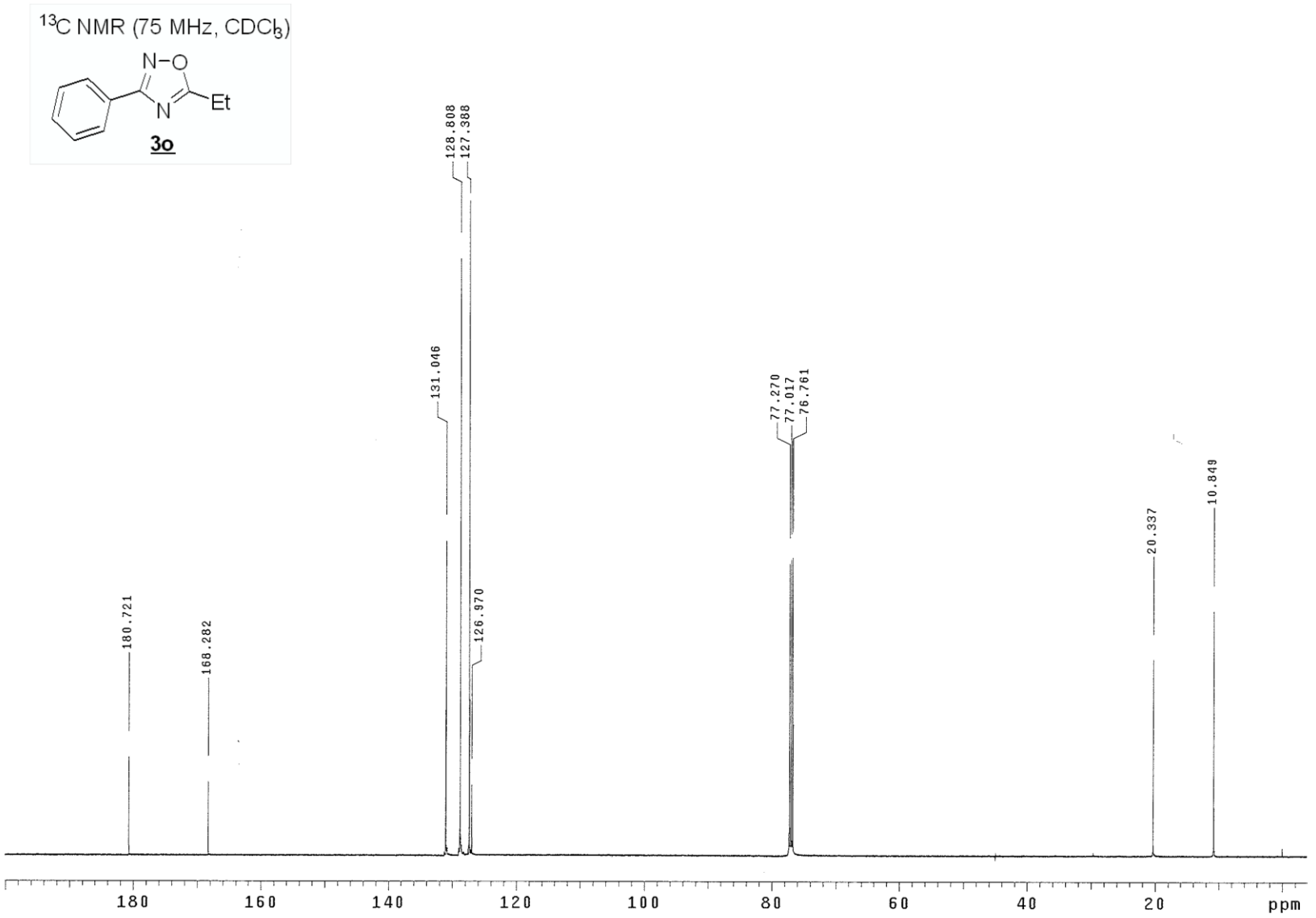


^{1}H NMR (500 MHz, $CDCl_3$)

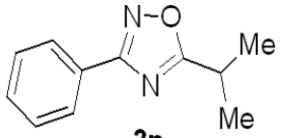


3o

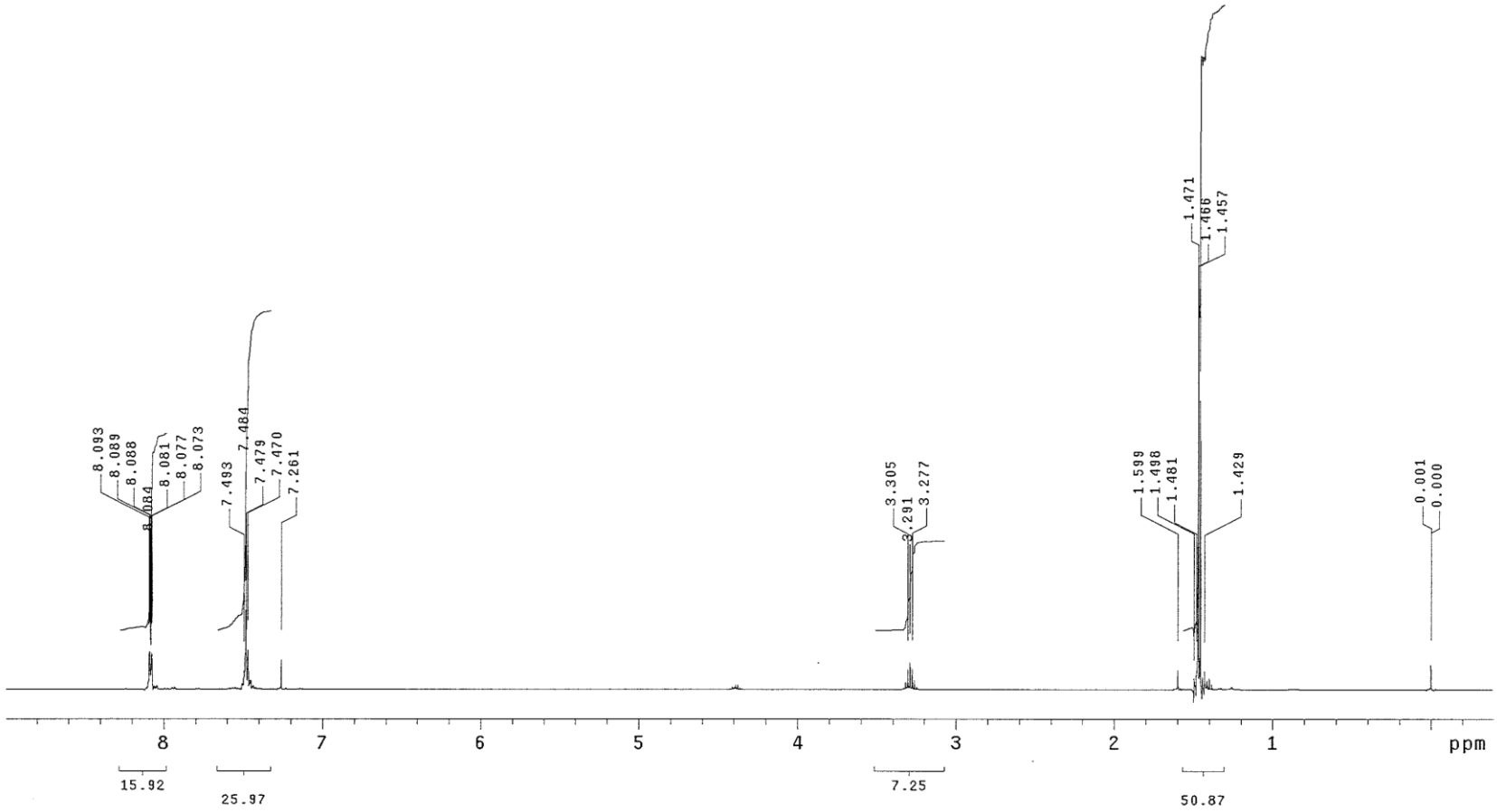


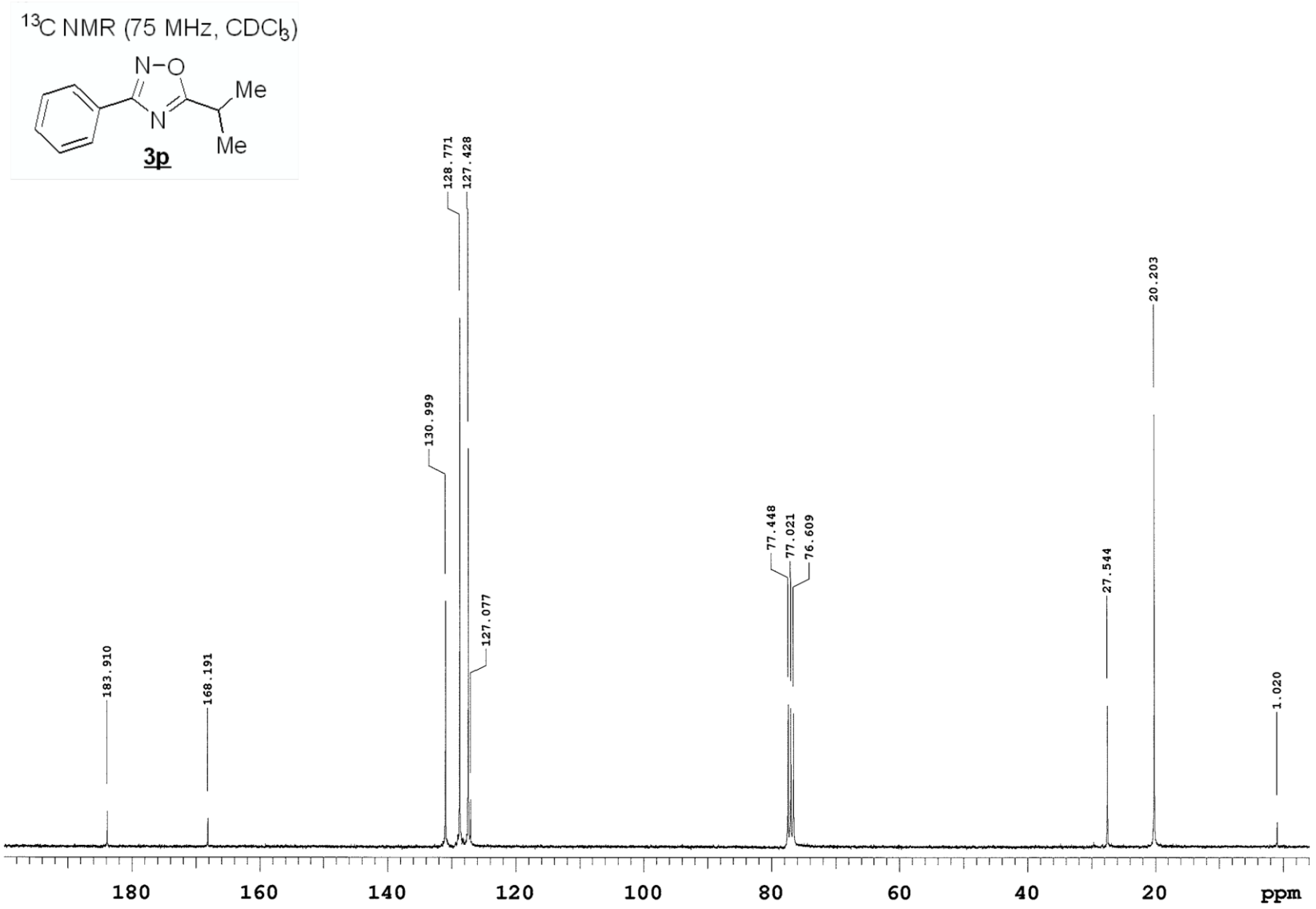

^{13}C NMR (75 MHz, CDCl$_3$)
N–O
N
Et
3o
180.721
168.282
131.046
128.808
127.388
126.970
77.270
77.017
76.761
20.337
10.849
180
160
140
120
100
80
60
40
20
ppm

^{1}H NMR (500 MHz, $CDCl_3$)

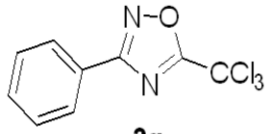


3p

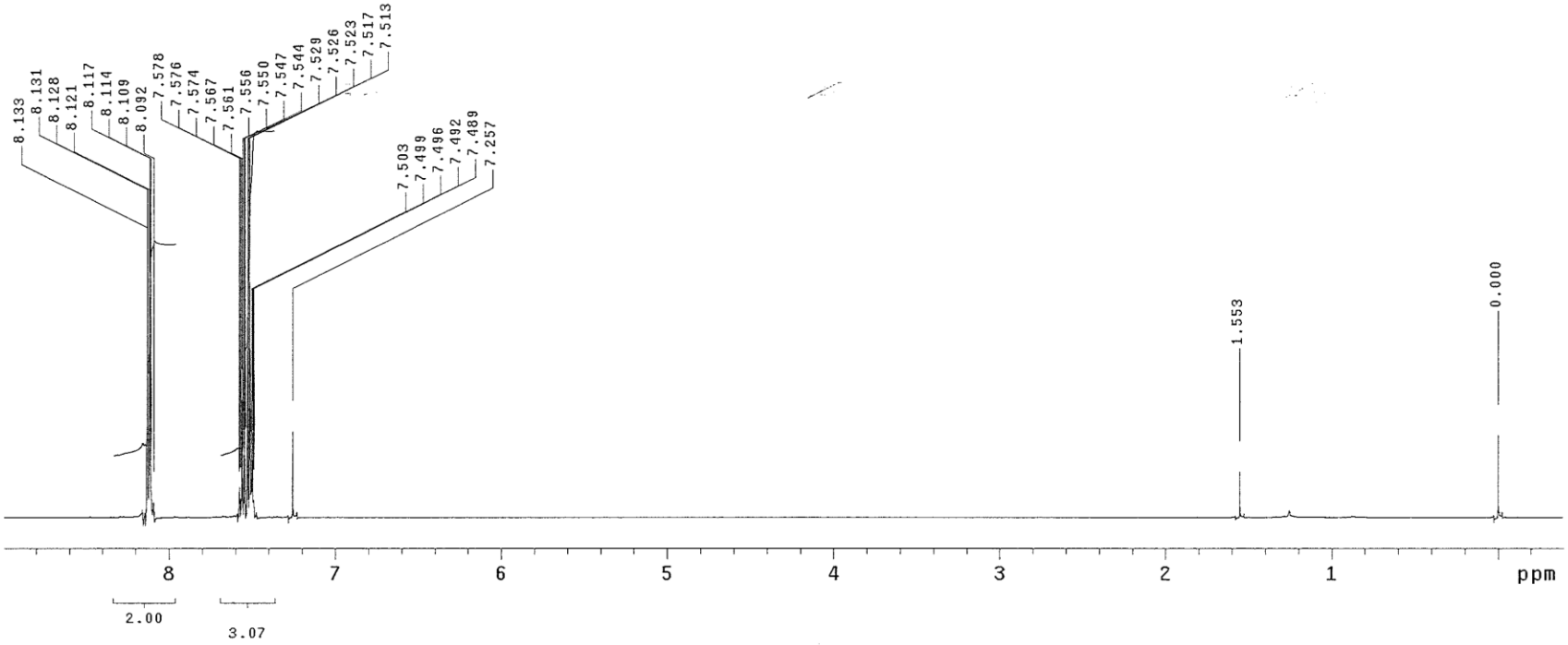


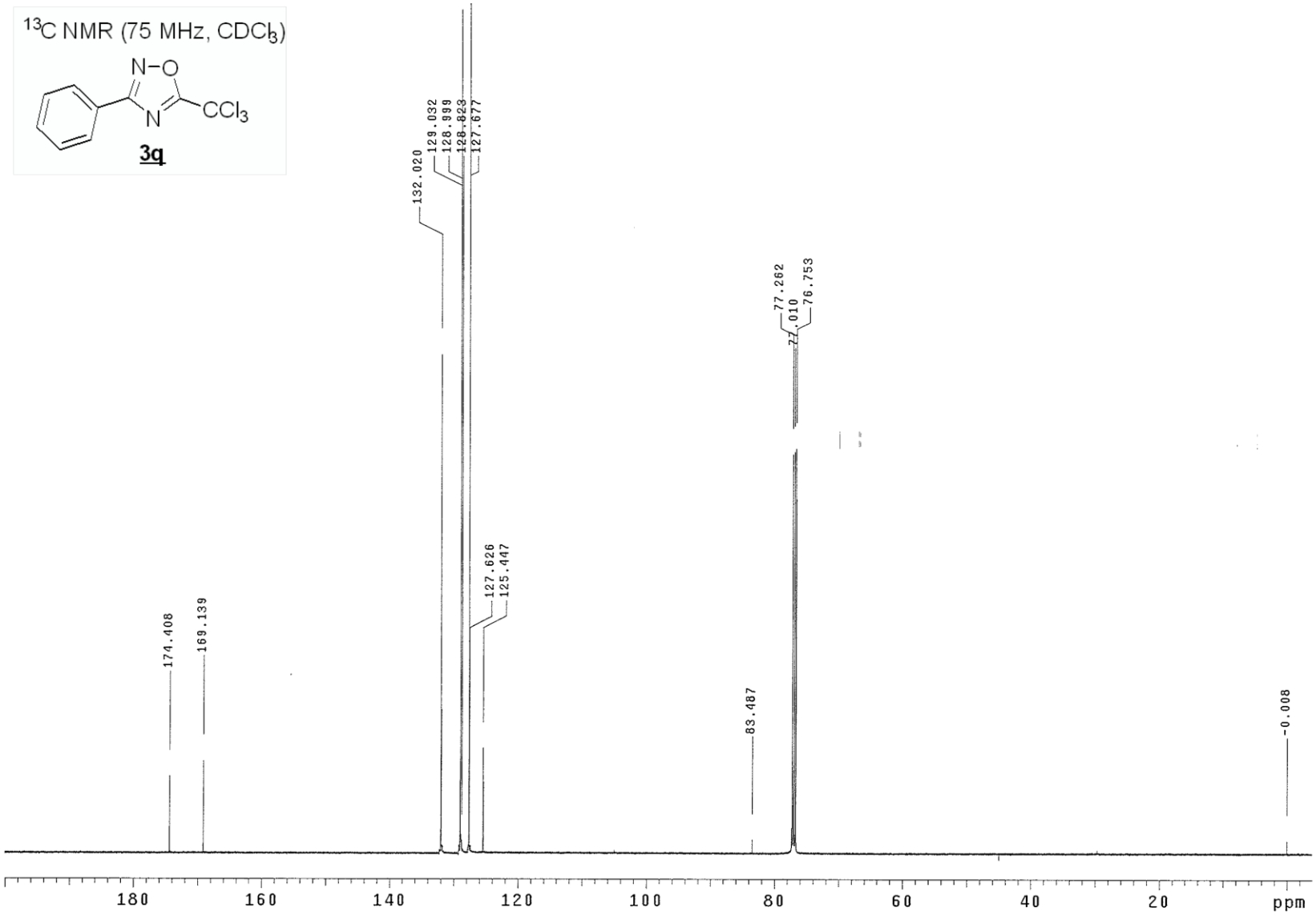

^{13}C NMR (75 MHz, CDCl$_3$)
N–O
Me
N
Me
3p
183.910
168.191
130.999
128.771
127.428
127.077
77.448
77.021
76.609
27.544
20.203
1.020
180
160
140
120
100
80
60
40
20
ppm

^{1}H NMR (500 MHz, $CDCl_3$)

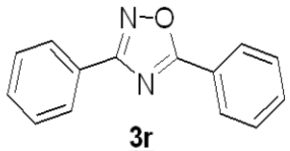


3q

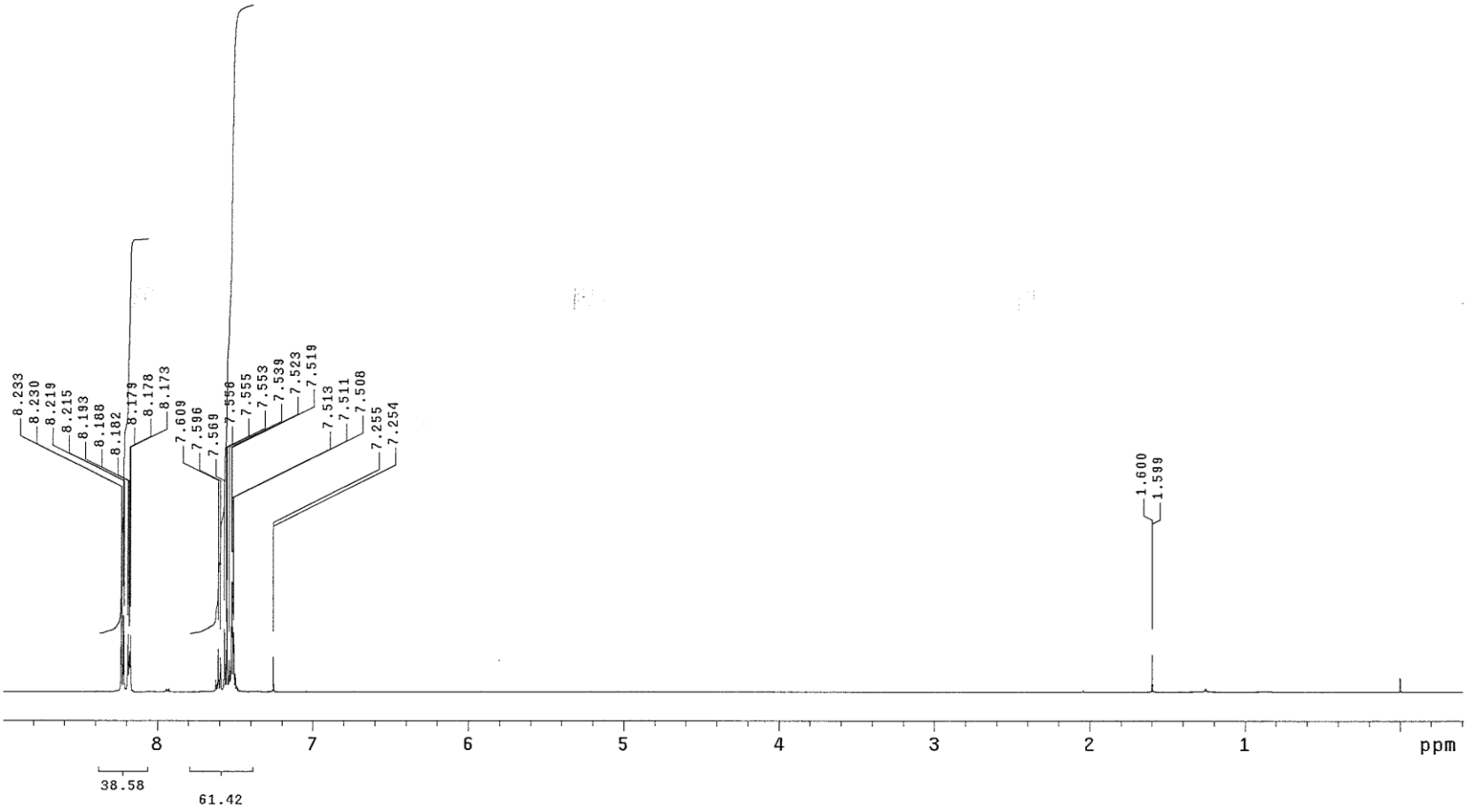



^{13}C NMR (75 MHz, CDCl$_3$)
N–O
N
CCl$_3$
3q
132.020
129.032
128.999
128.823
127.677
127.626
125.447
77.262
77.010
76.753
83.487
174.408
169.139
-0.008
180
160
140
120
100
80
60
40
20
ppm

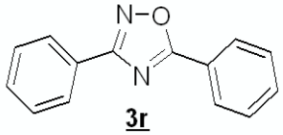
^{1}H NMR (500 MHz, $CDCl_3$)



3r

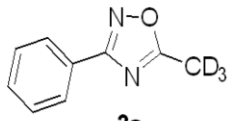


^{13}C NMR (75 MHz, $CDCl_3$)

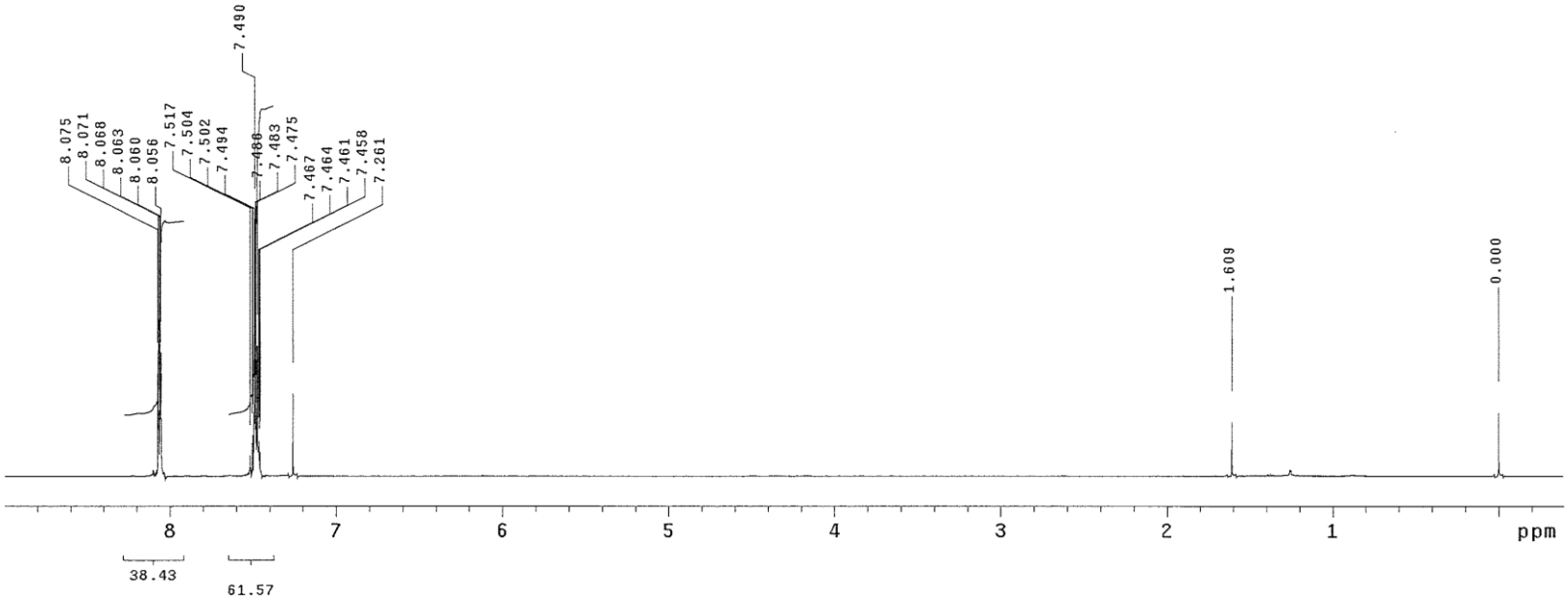


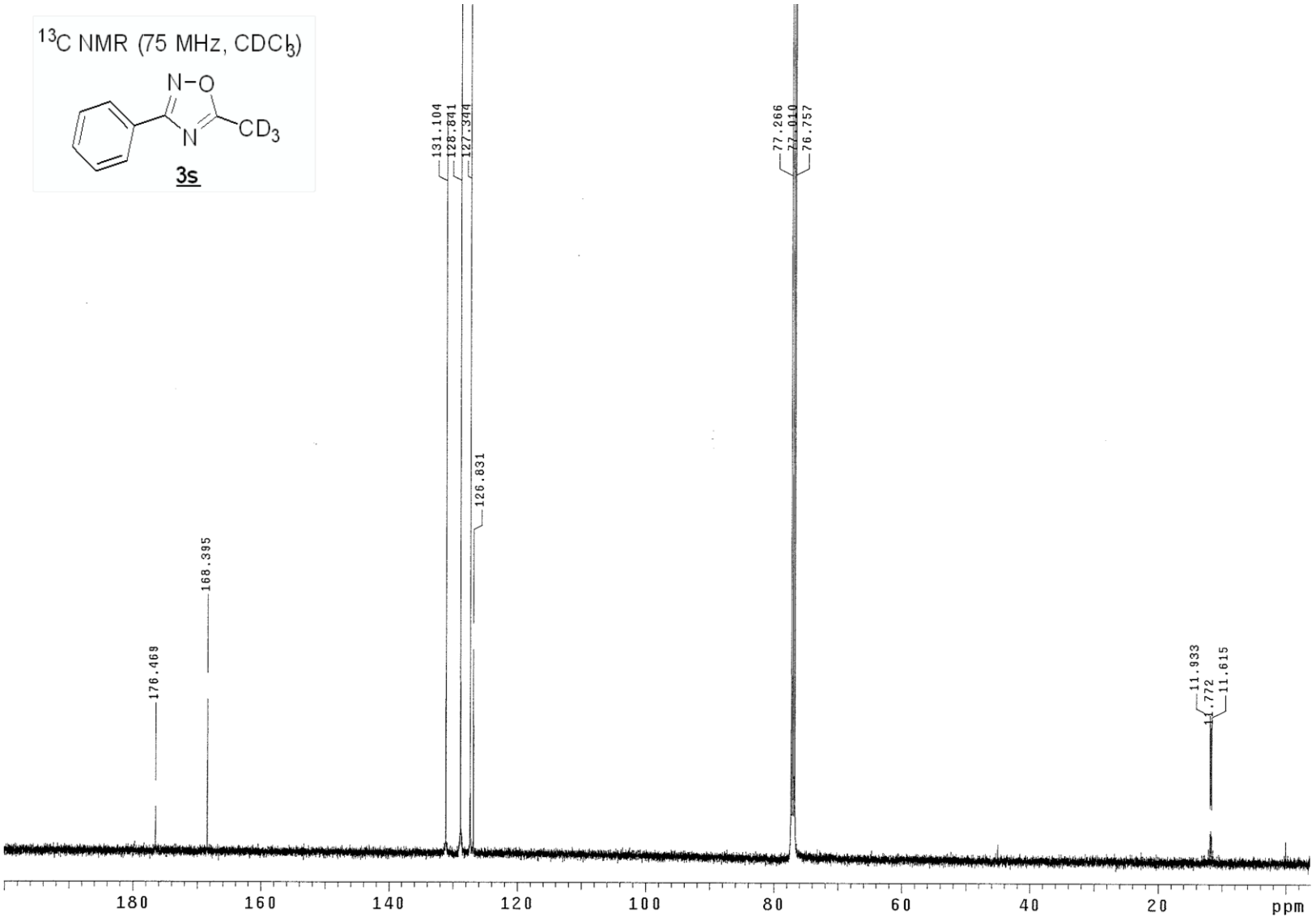
3r

^{1}H NMR (500 MHz, $CDCl_3$)

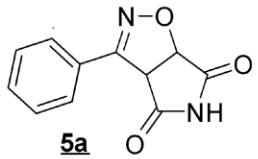


3s

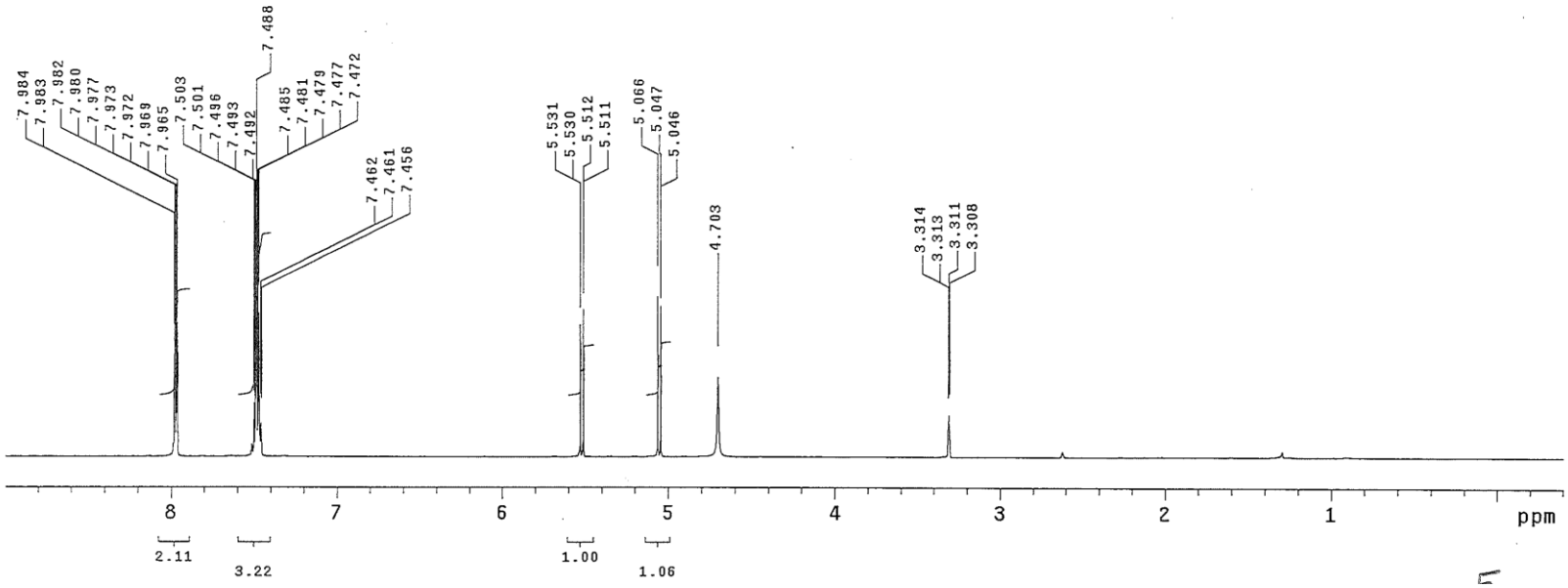



^{13}C NMR (75 MHz, $CDCl_3$)
N–O
N
CD_3
3s
131.104
128.841
127.344
126.831
77.266
77.010
76.757
176.469
168.395
11.933
11.772
11.615
180
160
140
120
100
80
60
40
20
ppm

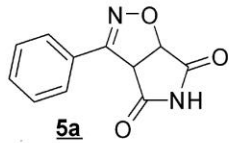
^{1}H NMR (500 MHz, CD_3OD-DMSO-*d6*)



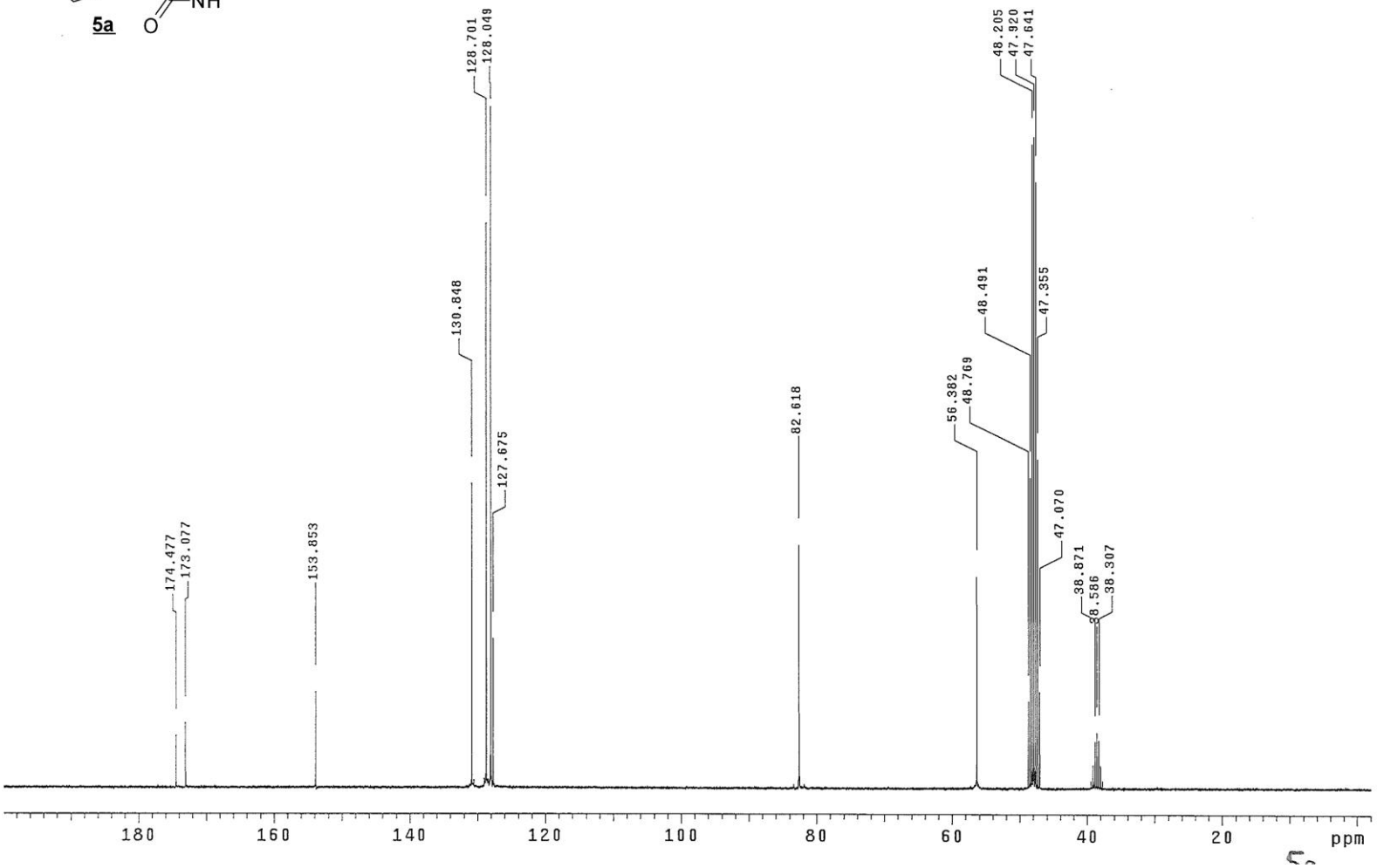
5a



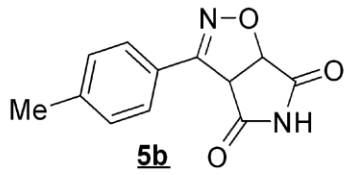
^{13}C NMR (75 MHz, CD_3OD/DMSO-*d6*)



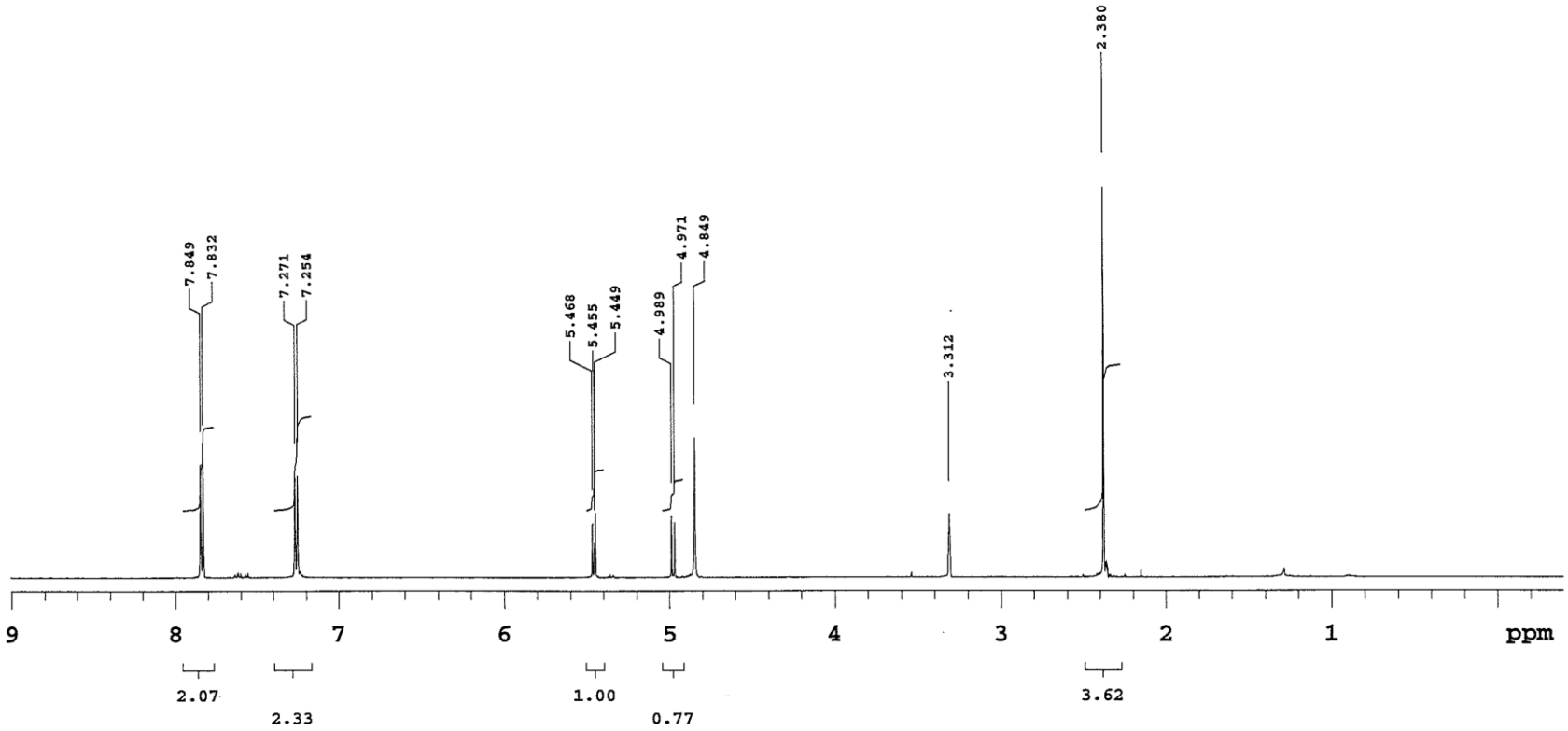
5a



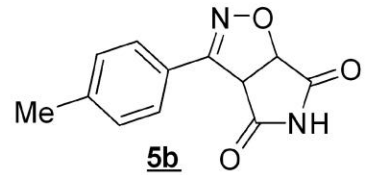
^{1}H NMR (500 MHz, CD_3OD)



5b

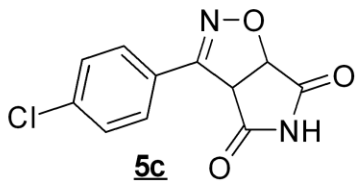


^{13}C NMR (75 MHz, CD_3OD)

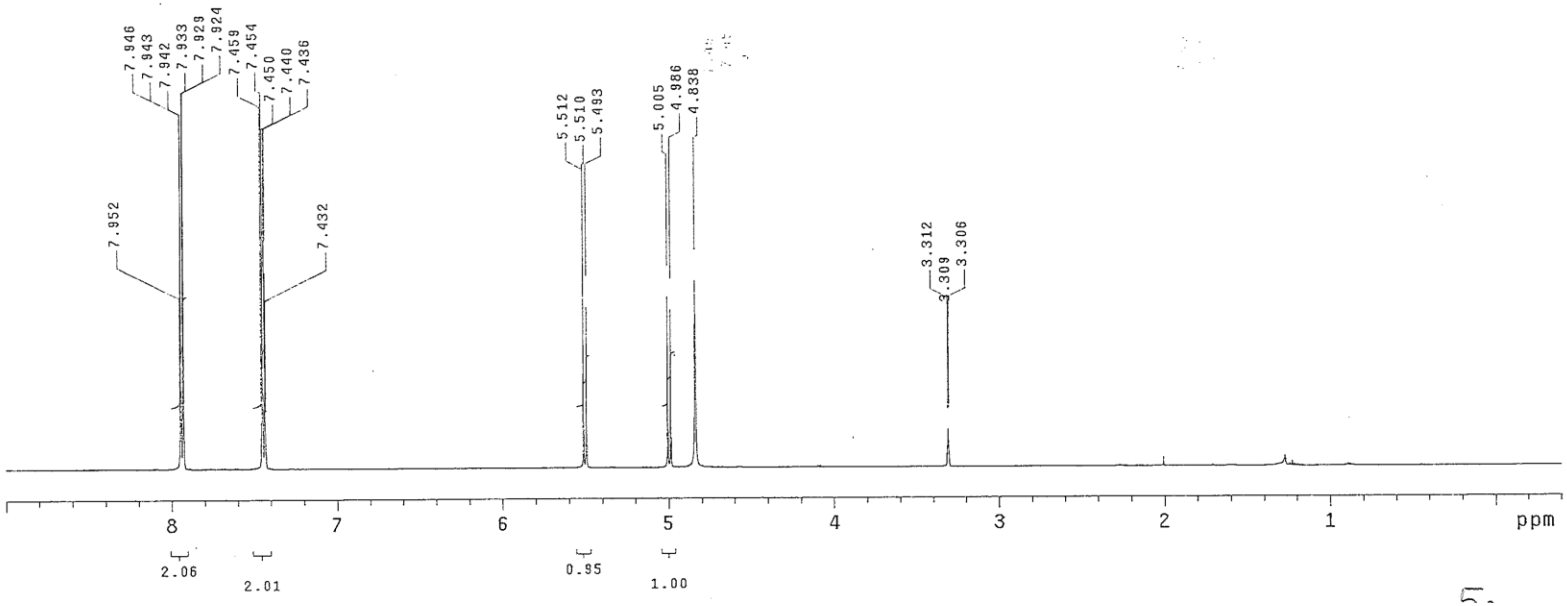


5b

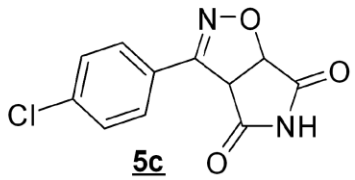
^{1}H NMR (500 MHz, CD_3OD)



5c

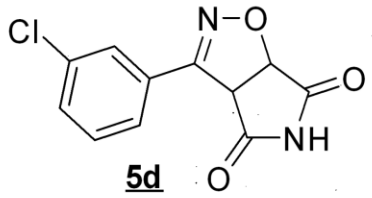


^{13}C NMR (75 MHz, CD_3OD)

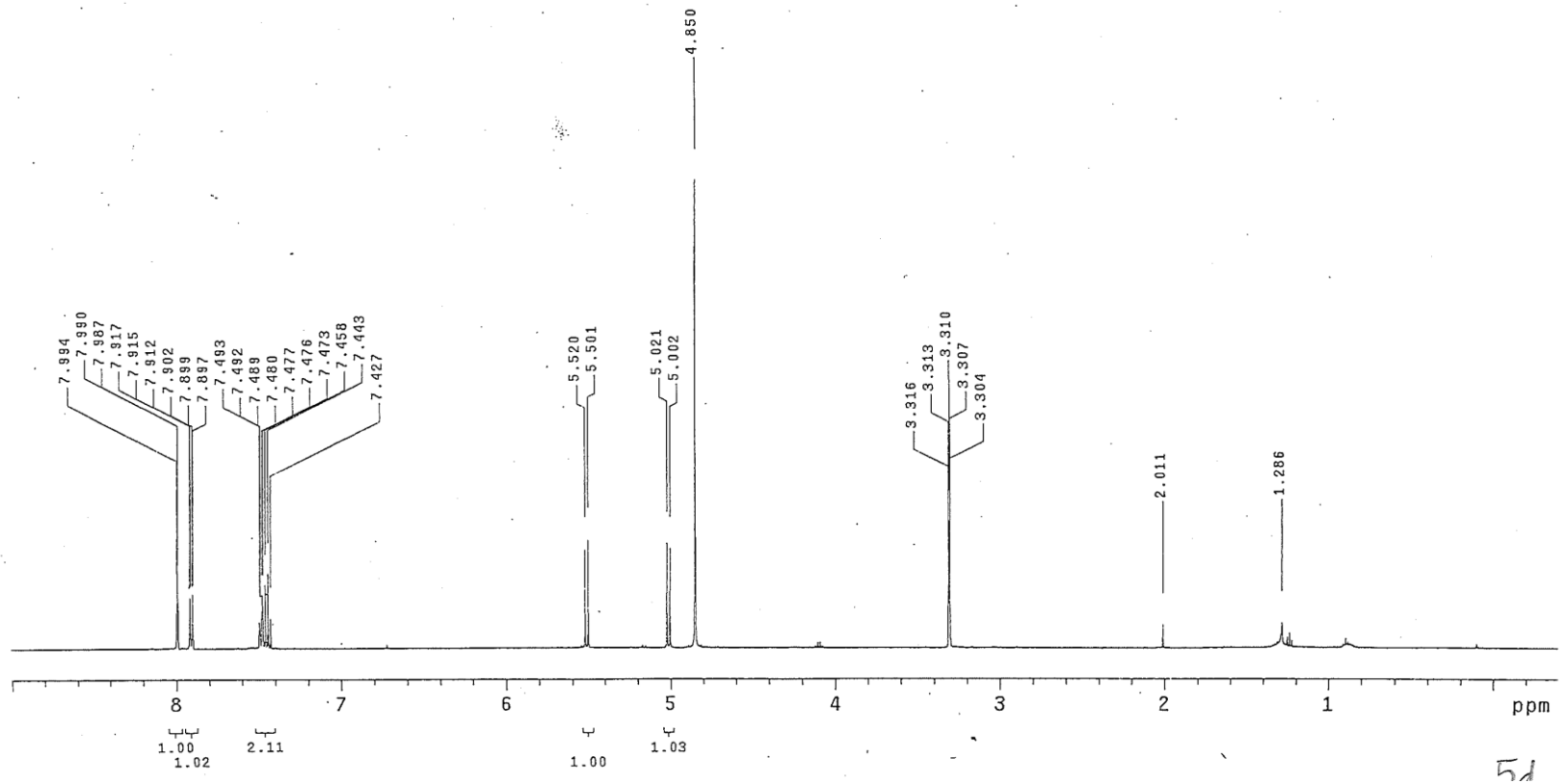


5c

^{1}H NMR (500 MHz, CD_3OD)

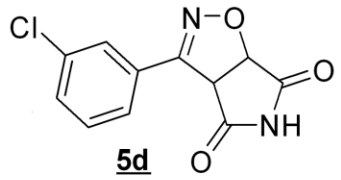


5d



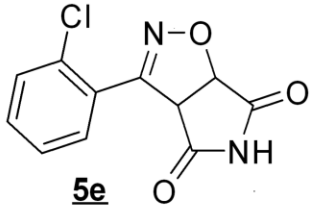
5d

^{13}C NMR (75 MHz, CD_3OD)

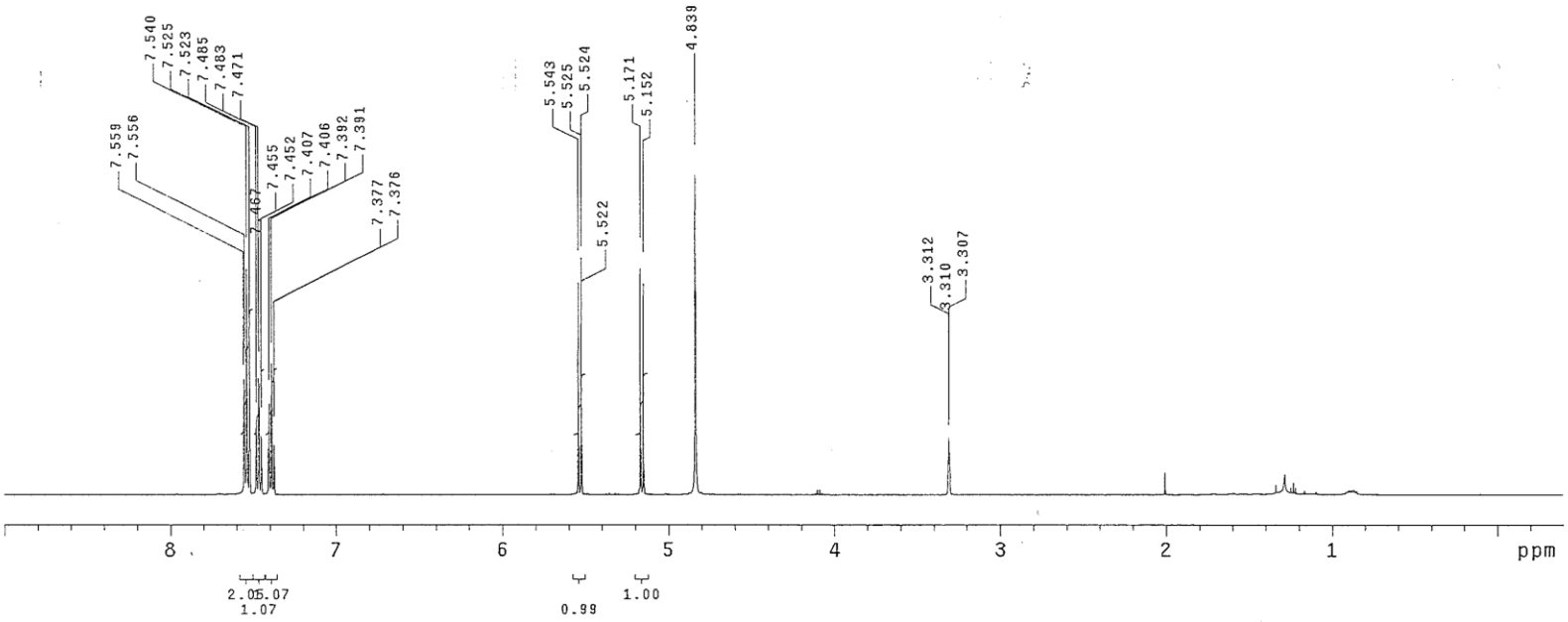


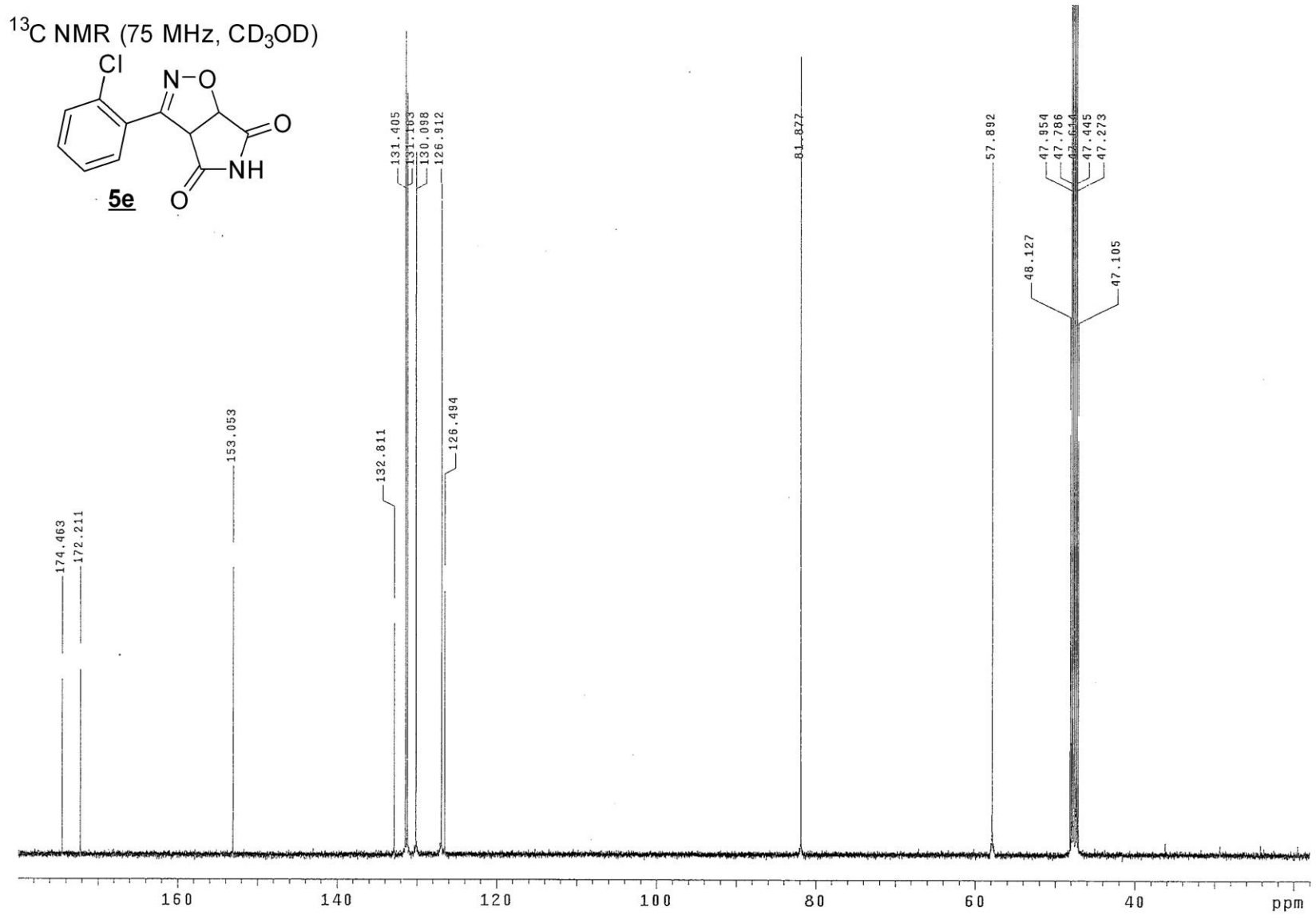
5d

^{1}H NMR (500 MHz, CD_3OD)

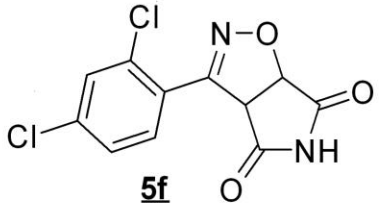


5e

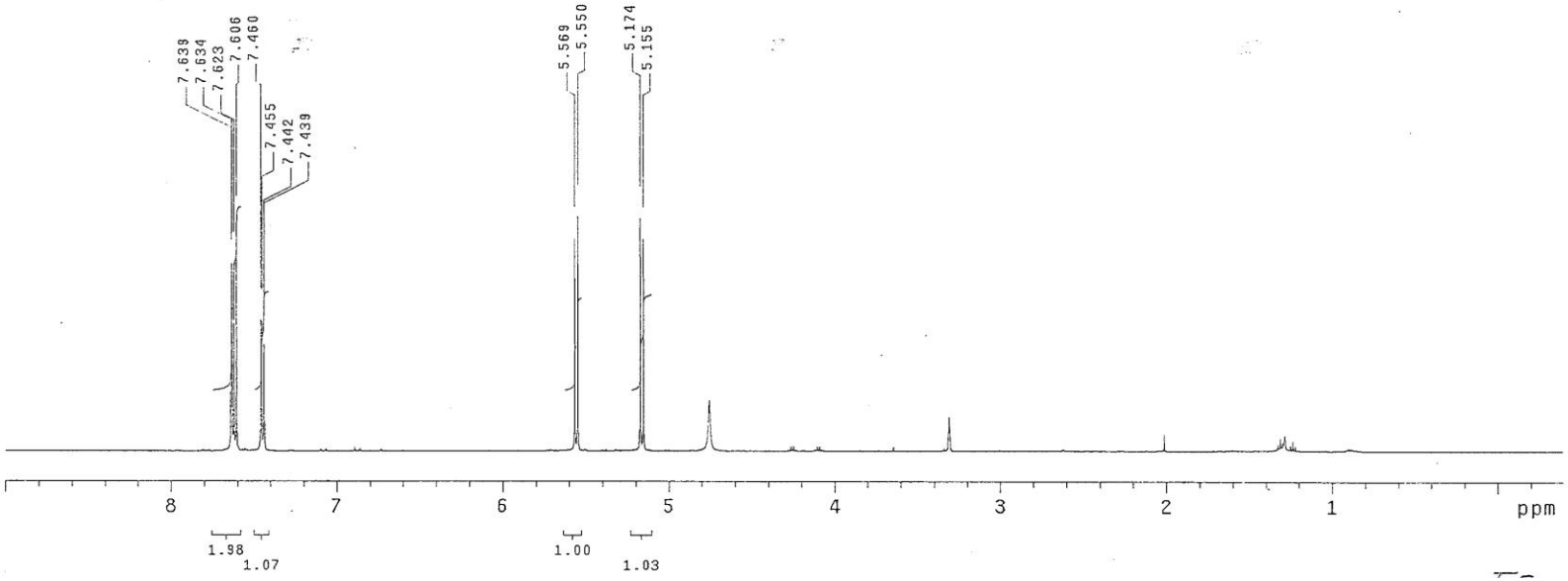


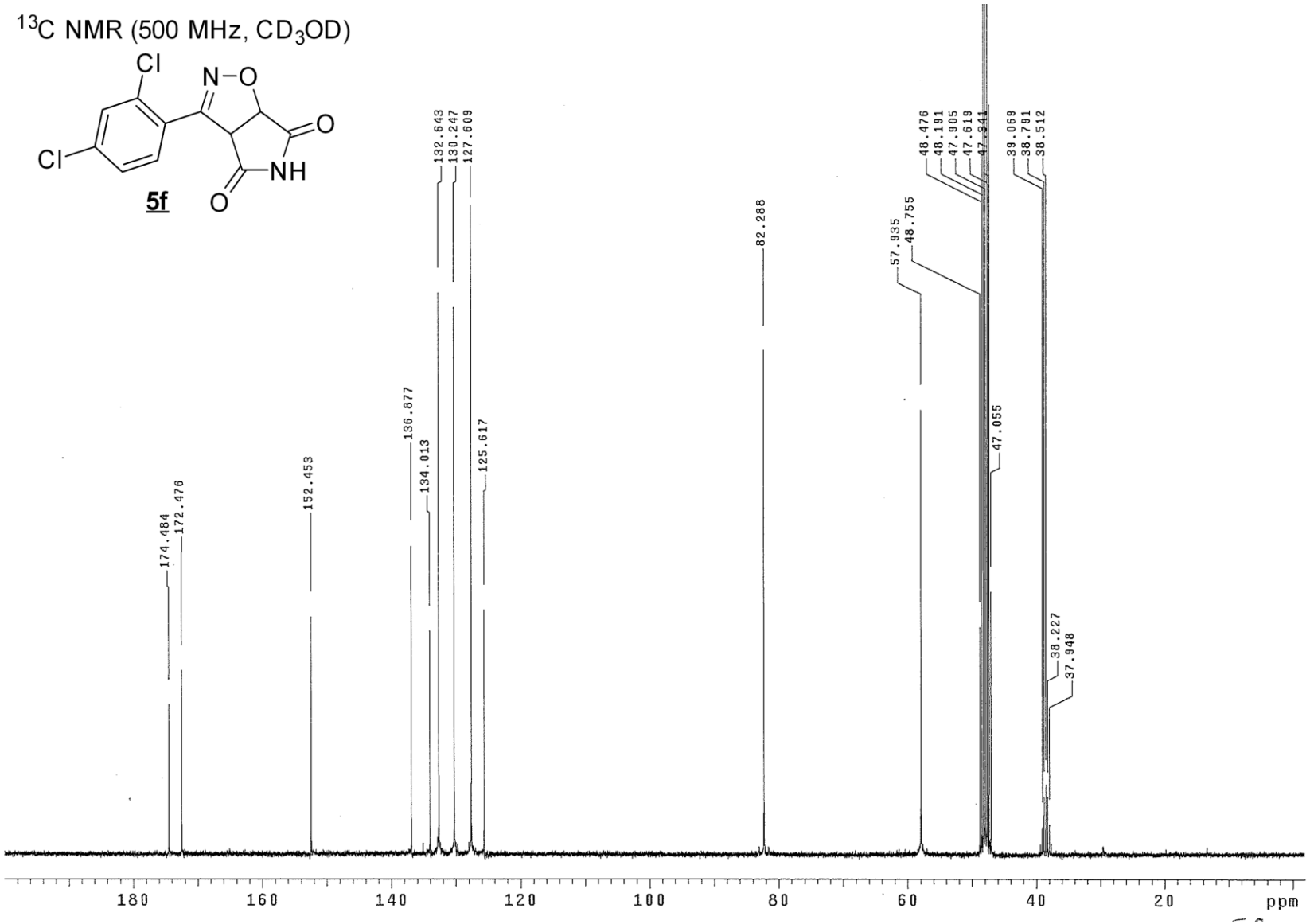

13C NMR (75 MHz, CD3OD)
Cl
N−O
O
NH
O
5e
174.463
172.211
153.053
132.811
131.405
131.103
130.098
126.912
126.494
81.877
57.892
48.127
47.954
47.786
47.614
47.445
47.273
47.105
160
140
120
100
80
60
40
ppm

^{1}H NMR (500 MHz, CD_3OD)



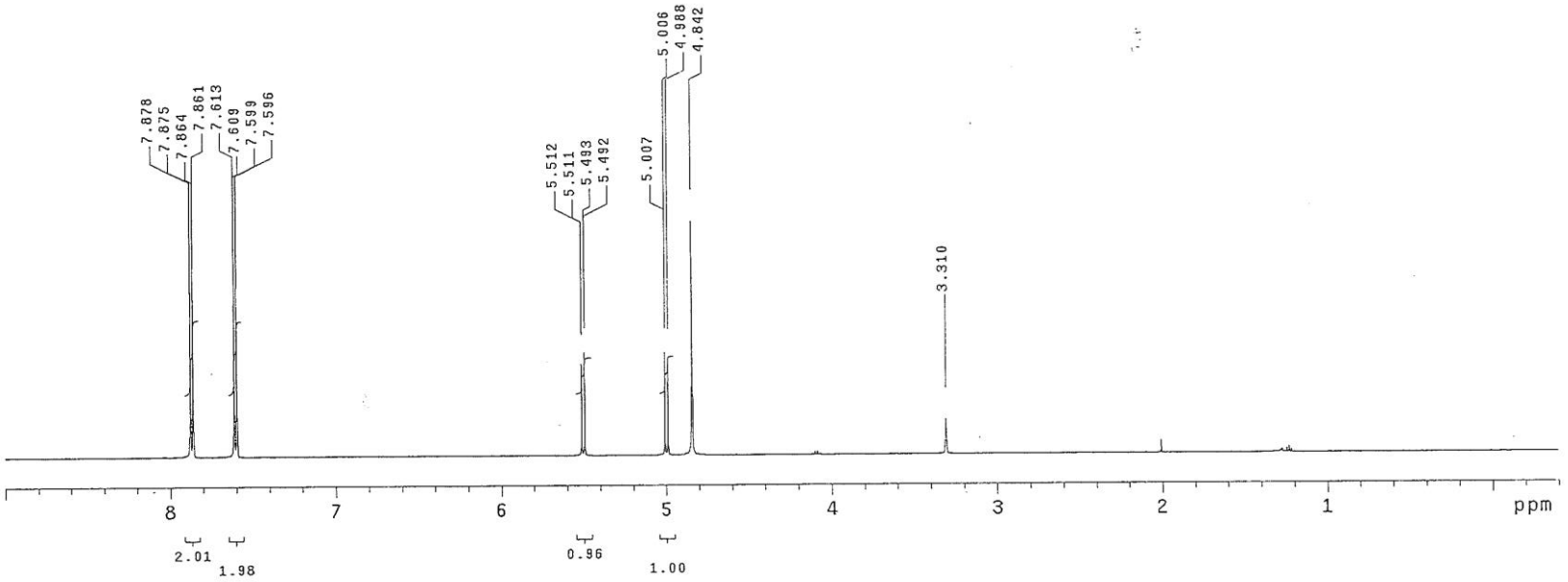
5f



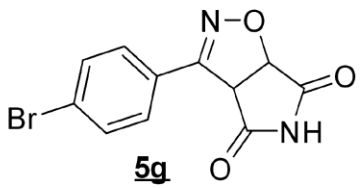

13C NMR (500 MHz, CD3OD)
Cl
N–O
O
Cl
NH
O
5f
174.484
172.476
152.453
136.877
134.013
132.643
130.247
127.609
125.617
82.288
57.935
48.755
48.476
48.191
47.905
47.619
47.341
47.055
39.069
38.781
38.512
38.227
37.948
180
160
140
120
100
80
60
40
20
ppm

^{1}H NMR (500 MHz, CD_3OD)

5g

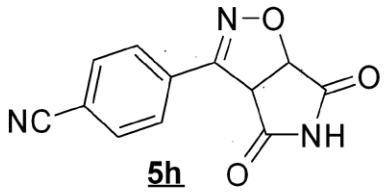


^{13}C NMR (500 MHz, CD_3OD)

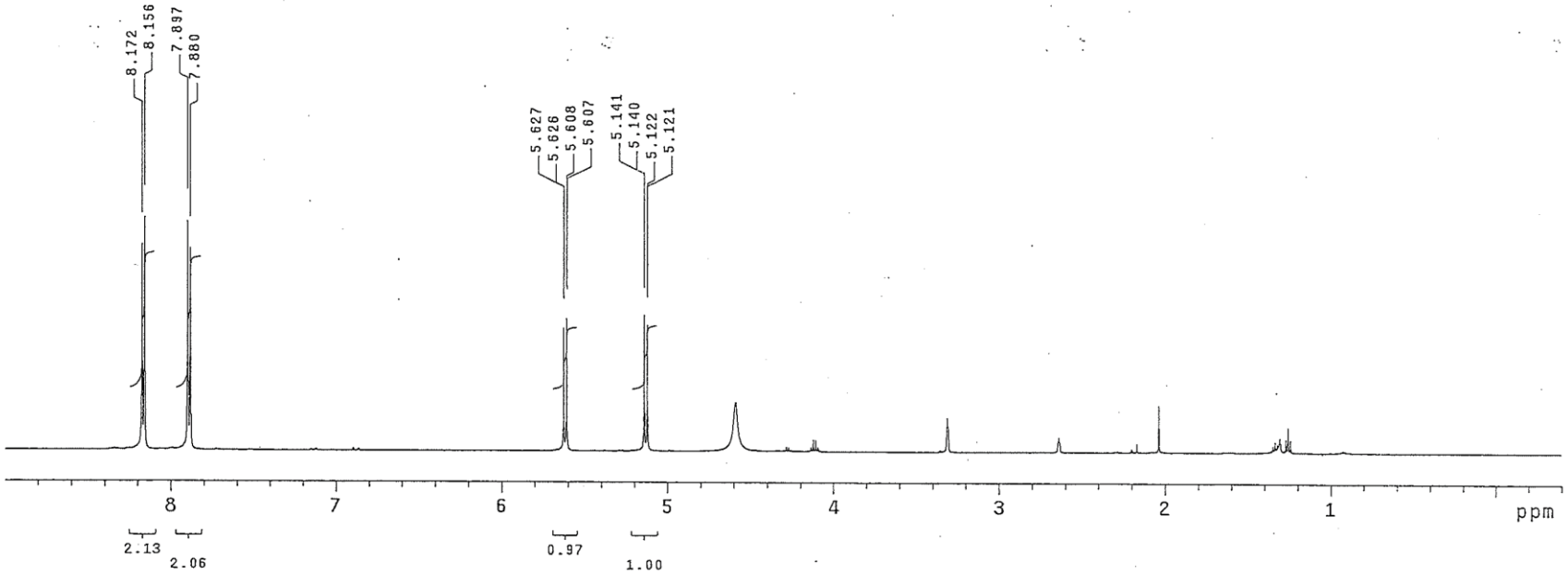


5g

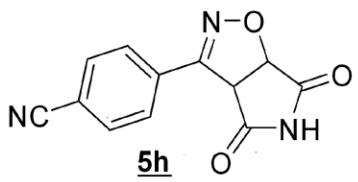
^{1}H NMR (500 MHz, CD_3OD/DMSO-*d6*)



5h

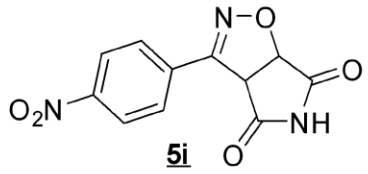


^{13}C NMR (75 MHz, CD_3OD/DMSO-*d6*)

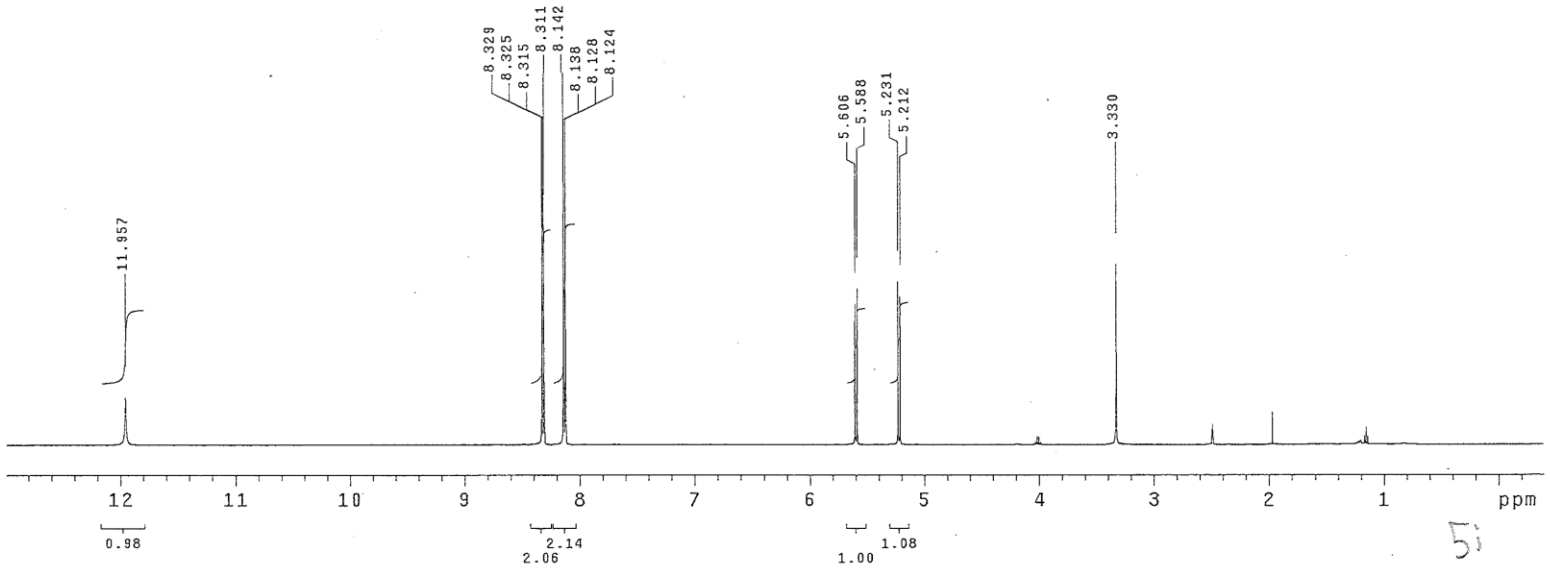


5h

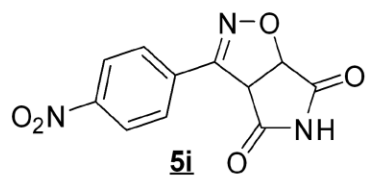
^{1}H NMR (500 MHz, DMSO-*d6*)



5i

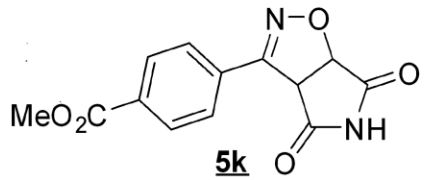


^{13}C NMR (75 MHz, DMSO-*d6*)

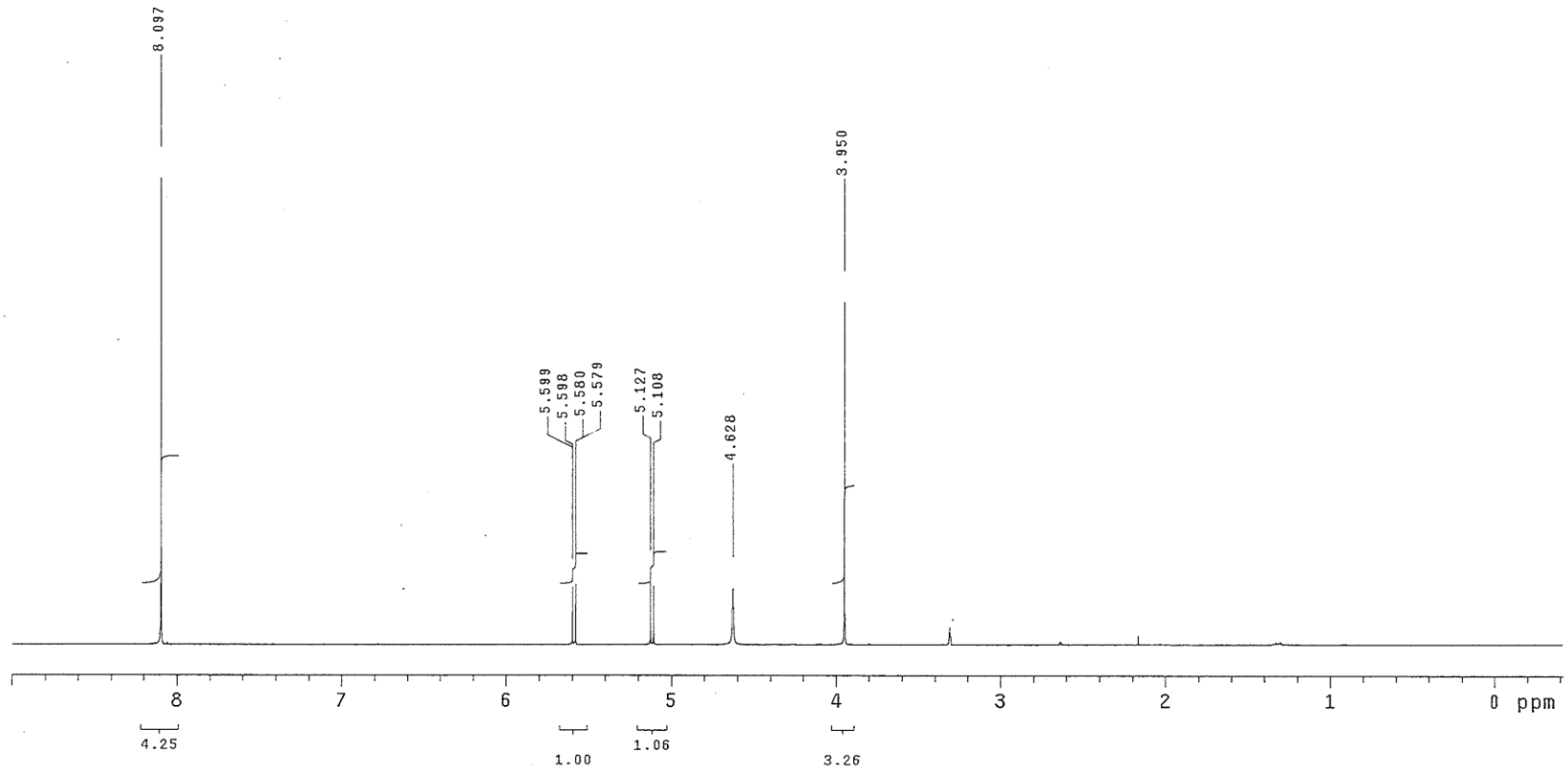


5i

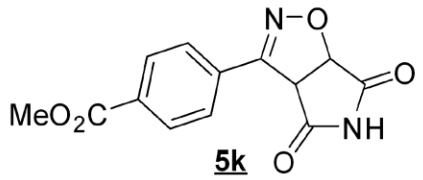
^{1}H NMR (500 MHz, CD_3OD/DMSO-*d6*)



5k

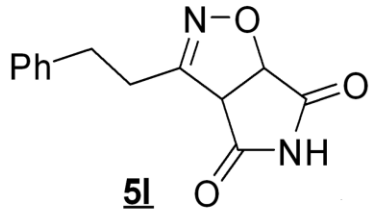


^{13}C NMR (75 MHz, CD_3OD/DMSO-*d6*)



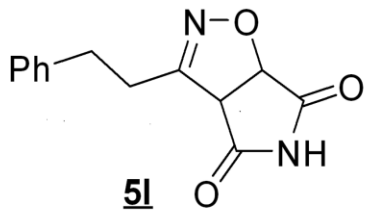
5k

^{1}H NMR (500 MHz, CD_3OD)



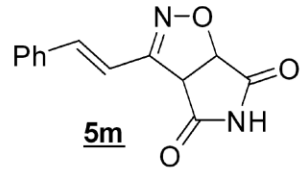
5l

^{13}C NMR (75 MHz, CD_3OD)

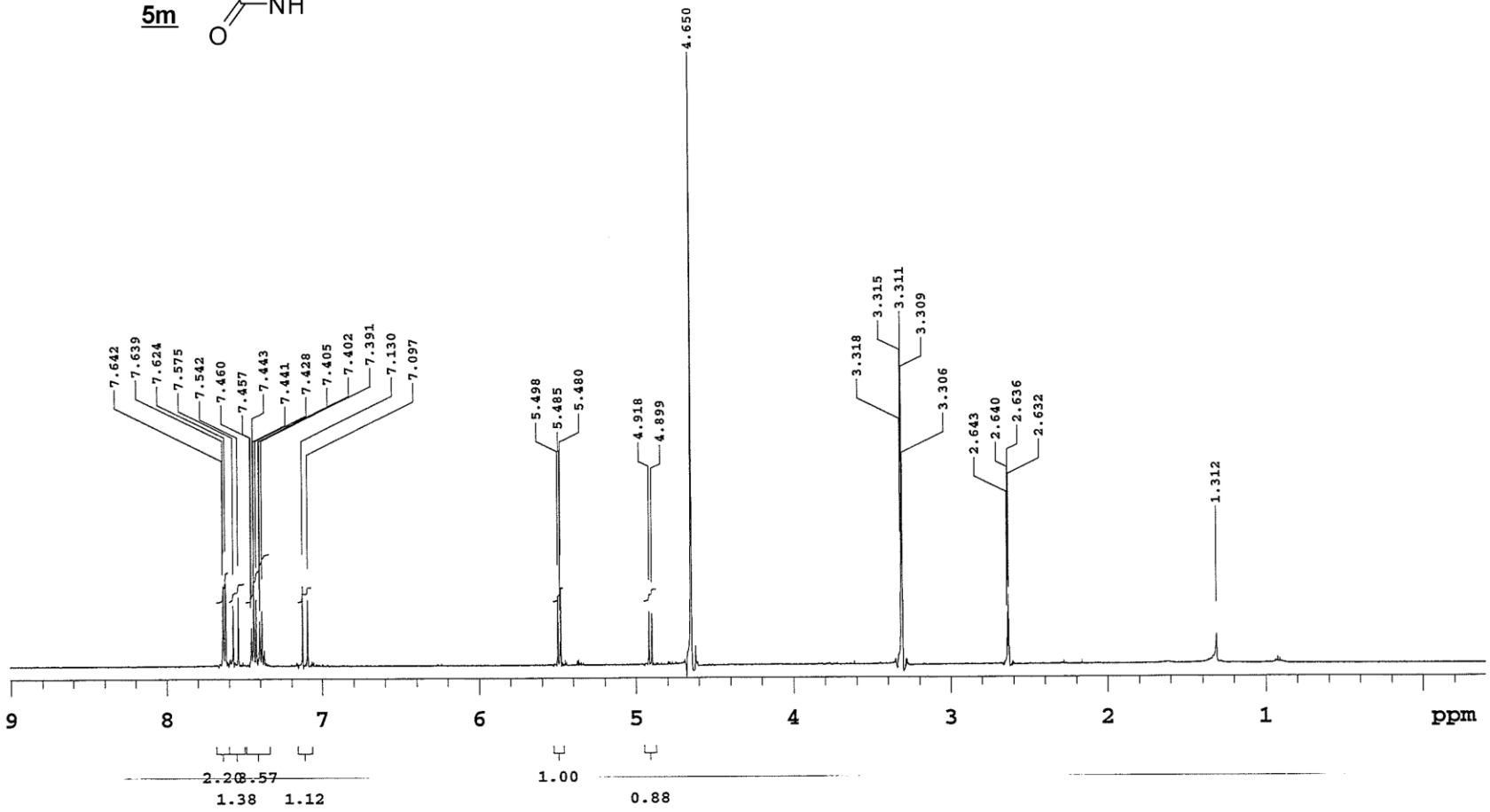


5l

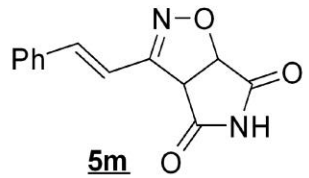
^{1}H NMR (500 MHz, CD_3OD/DMSO-*d6*)



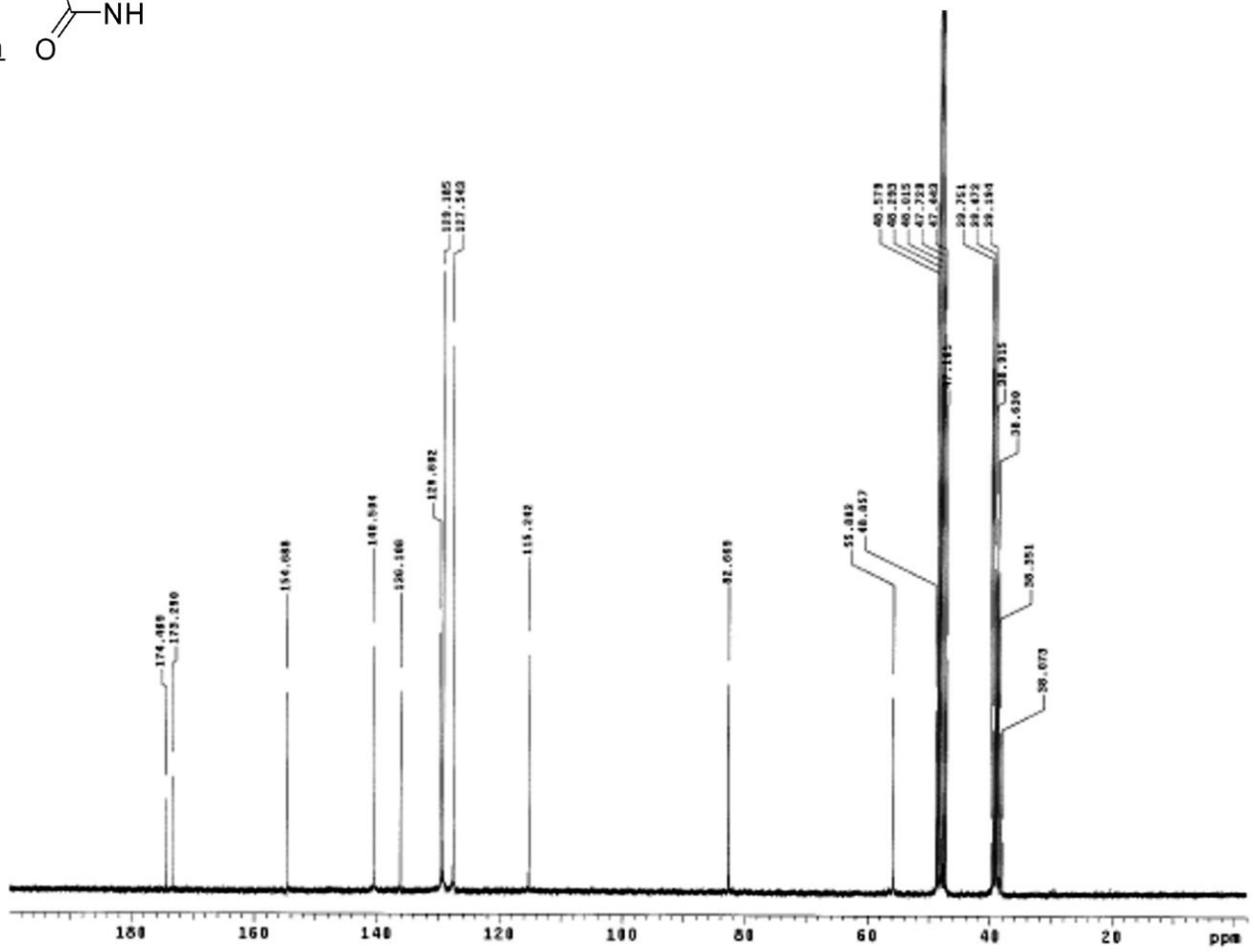
5m



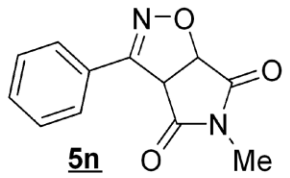
^{13}C NMR (75 MHz, CD_3OD/DMSO-*d6*)



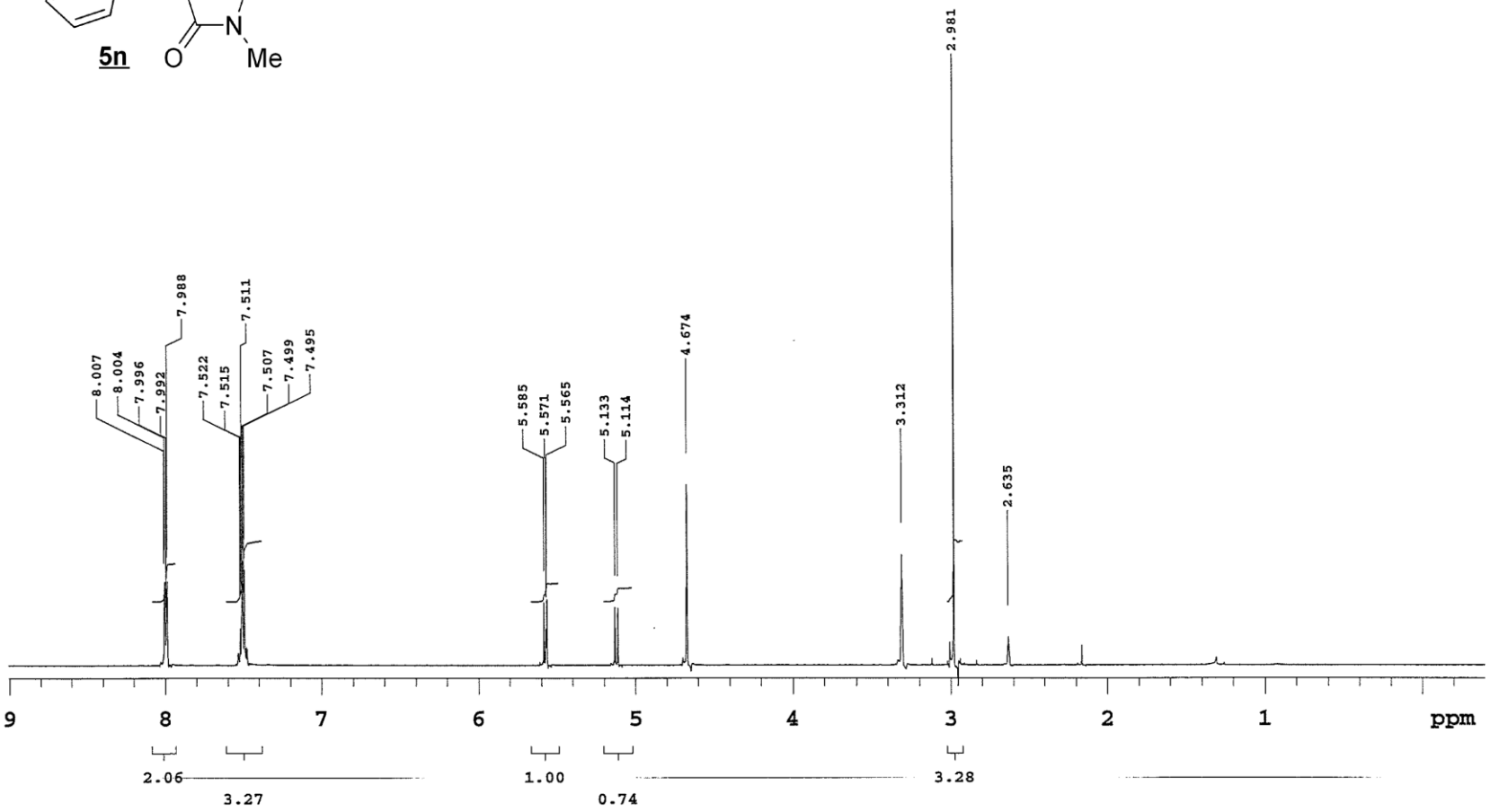
5m



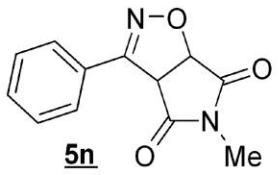
^{1}H NMR (500 MHz, CD_3OD/DMSO-*d6*)



5n



^{13}C NMR (75 MHz, CD_3OD/DMSO-*d6*)



5n

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